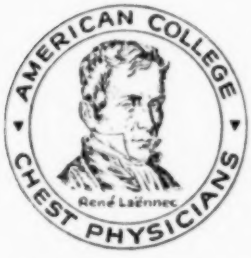
VOLUME XXIII NUMBER 6

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



PUBLISHED MONTHLY

JUNE
1953

INDEX NUMBER

PUBLICATION OFFICE, ALAMOGORDO ROAD, EL PASO, TEXAS
EXECUTIVE OFFICE, 112 EAST CHESTNUT STREET, CHICAGO 11, ILLINOIS

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DISEASES *of the* CHEST

OFFICIAL PUBLICATION
OF THE
AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
112 East Chestnut Street, Chicago 11, Illinois
MURRAY KORNFELD, *Managing Editor*

VOLUME XXIII JUNE 1953 NUMBER 6

CONTENTS:

Entered as second class matter, August 18, 1936, at the postoffice at El Paso, Tex., under the Act of August 24, 1912

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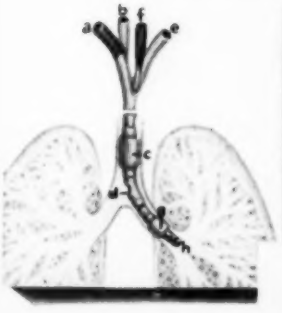

a. To spirometer for right lung
b. For inflation of upper balloon
c. Balloon occluding trachea
d. Air from right lung
e. To spirometer for left lung
f. For inflation of lower balloon
g. Balloon occluding left bronchus
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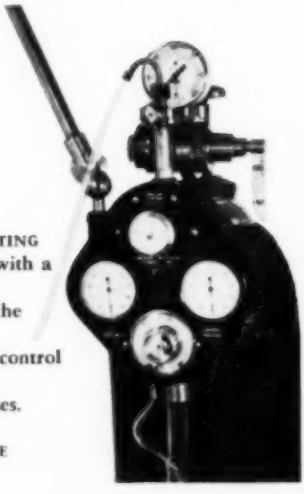

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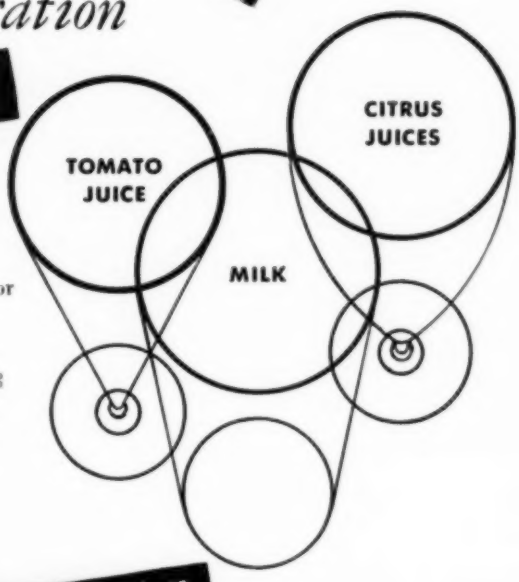

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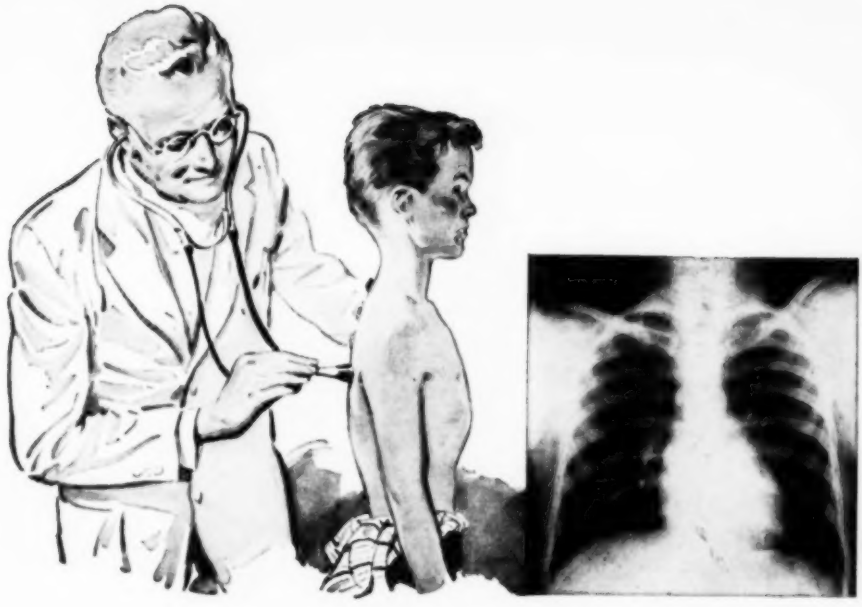

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DISEASES *of the* CHEST

VOLUME XXIII JUNE 1953 NUMBER 6

Pulmonary Function and Circulatory Dynamics in Artificial Pneumoperitoneum*

I. Studies on Patients with Pneumoperitoneum Therapy for Pulmonary Tuberculosis.

ROSS C. KORY, M.D., DAN C. ROEHM, M.D.,
GEORGE R. MENEELY, M.D., F.C.C.P. and ROBERT A. GOODWIN, JR., M.D.
Nashville, Tennessee

Artificial pneumoperitoneum was first reported in 1893 by von Mosetig-Moorhof[1] and independently by Nolen[2] in the same year as a therapeutic measure in tuberculous peritonitis. Reich[3] in 1924 first described the use of pneumoperitoneum in treating pulmonary emphysema. Banyai[4] reported the accidental induction in 1931 of pneumoperitoneum instead of pneumothorax in a patient with severe intermittent pulmonary hemorrhage, with dramatic cessation of bleeding after pneumoperitoneum. Since that time Banyai has been one of the chief advocates of this measure, and his monograph[5] discusses in detail the various aspects of the procedure. In the past decade pneumoperitoneum has enjoyed an increasingly widespread use as a form of collapse therapy in pulmonary tuberculosis and in some centers has completely replaced pneumothorax. Several clinical reports on large numbers of patients[6-9] have attested to the therapeutic usefulness of this procedure.

The physiologic effects of pneumoperitoneum on either the respiratory or the cardiovascular system have received little attention. Ricci and Irelli[10] found a fall in venous pressure four to six hours after induction of pneumoperitoneum. They observed no changes in arterial pressure, pulse rate, or respiratory rate. Risi,[11] investigating experimental pneumoperitoneum in dogs, found some decrease in respiratory rate following pneumoperitoneum but no change in blood pressure, heart rate, or type of respiration. Banyai[5] found no changes in blood pressure ascribable to pneumoperitoneum in 44 patients followed as long as one year. Elwood, Piltz and Potter[12] firmly established the relationship between elevation of the left diaphragm (either alone or together with the right), a more transverse anatomical position of the heart, and the electrocardiographic pattern of left axis deviation with T wave inversion in lead III. Additional elevation

*From the Research Laboratory, Medical and Tuberculosis Service, Thayer Veterans Administration Hospital and the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

of the right diaphragm (from a right phrenic nerve operation) caused loss or lessening of the left axis deviation with T_3 becoming upright.

Several studies of vital capacity[13,14,5] have indicated that 55 to 80 per cent of the patients show a slightly decreased vital capacity after pneumoperitoneum, the decrease ranging from 12 to 15 per cent. Wright, Place, and Princi[15] in a study of 19 patients with pulmonary tuberculosis found that pneumoperitoneum causes marked reduction in functional residual capacity, residual air, and total capacity of subjects in the erect position, with a similar but quantitatively less marked effect with the patient recumbent. The superimposition of an abdominal binder caused a further decrease primarily in the vital capacity. The maximum breathing capacity was only slightly reduced by the induction of pneumoperitoneum. More recently Leiner and Abramowitz[16] studied 16 patients spirometrically before and from one to 13 months after induction of pneumoperitoneum. They reported slight decreases in oxygen consumption, maximum breathing capacity, and ventilatory reserve; slight increases in resting minute ventilation, tidal air, and ventilatory equivalents; and no significant changes in the vital capacity or respiratory rate. The observed changes became smaller as the pneumoperitoneum was continued and values tended to return to pretreatment levels.

The present study was undertaken: (a) to extend the quantitative pulmonary function data on the effect of pneumoperitoneum as employed in pulmonary tuberculosis, by the addition of measurements of respiratory gases, arterial blood, dead space and oxygen removal in addition to lung volume and ventilatory studies, and (b) to determine how, if at all, pneumoperitoneum affects the heart and circulation. In a procedure employed so widely as is pneumoperitoneum, the possible physiological effects certainly deserve investigation. However, these data also serve a second purpose by establishing a basis for comparison in studying the cardio-respiratory effects of pneumoperitoneum when used as a therapeutic measure in pulmonary emphysema.[17]

Methods

Lung volume measurements were done with the patient recumbent or semi-reclining. The Inspiratory Capacity (IC) and Expiratory Reserve (ER) were measured by direct spirography, the sum of these two values constituting the vital capacity (VC). The functional residual capacity (FRC) was determined in duplicate by a modified helium dilution technique.[18,19] Maximum breathing capacity (MBC) was measured by means of a high velocity, low resistance valve connected directly to a balanced Tissot spirometer. The voluntary hyperventilation period was 15 seconds, with determinations done in triplicate, the highest value being used. Resting minute ventilation (RMV), respiratory rate and tidal volume were measured in duplicate with patient in the basal state. Gas volumes were corrected to 760 mm. of Hg and 37 degrees C. (wet) and are expressed in liters per minute. Predicted values for both maximum breathing capacity and lung volumes were based on the regression formulae of Baldwin et al.[20] Phys-

iologic dead space was measured by the technique of Rahn et al.[21] with a continuous gas analyzer.

Right heart catheterization was carried out by the method of Cournand et al.,[22,23] with measurement of pressures by means of a strain gauge transducer recorded on a four channel direct writing recorder. Pressures measured included pulmonary "capillary," pulmonary artery, right ventricle, right auricle and superior vena cava. In one patient pressures were measured in the iliac veins and in the inferior vena cava first at the level of the renal veins and then just above the diaphragm. Cardiac output was determined by the direct Fick method with three minute Douglas bag collections of expired air analyzed by the method of Haldane.

Arterial blood, obtained from an indwelling needle in the brachial artery, and mixed venous (catheter) blood samples were collected by the technique of Riley[24] and analyzed for O_2 and CO_2 contents on the Van Slyke-Neill apparatus. Arterial blood pH determinations were carried out on some patients but not in all. The arterial CO_2 tension was calculated from the nomogram of Singer and Hastings[25] using either the measured or an assumed normal blood pH.

The following calculated values used in this report are derived as follows:

a) Air velocity index $= \frac{\text{Per cent Predicted MBC}}{\text{Per cent Predicted V.C.}}$
(Normal = 1.0 – 1.2)

b) Total Peripheral
Resistance (TPR) $= \frac{\text{BAm} - \text{RAm}}{\text{CO}} \times 1332$ dynes seconds cm.$^{-5}$

c) Total Pulmonary
Resistance (TPulR) $= \frac{\text{PAm} - \text{O}}{\text{CO}} \times 1332$ dynes seconds cm.$^{-5}$

d) Pulmonary Arteriolar
Resistance (PAR) $= \frac{\text{PAm} - \text{"PC"m}}{\text{CO}} \times 1332$ dynes seconds cm.$^{-5}$

e) Left ventricular work against pressure = W/L.
$$\text{W/L} = \frac{(\text{CI} \times 1.055)(\text{BAm} - 5) \times 13.6}{1,000} \text{ Kg.M./min./M}^2 \text{ B.S.A.}$$

f) Right ventricular work against pressure = W/R.
$$\text{W/R} = \frac{(\text{CI} \times 1.055)(\text{PAm} - \text{RAm}) \times 13.6}{1,000} \text{ Kg.M./min./M}^2 \text{ B.S.A.}$$

Where BAm = Brachial arterial mean pressure in mm.Hg.
RAm = Right auricular mean pressure in mm.Hg.
PAm = Pulmonary arterial mean pressure in mm.Hg.
PCm = Pulmonary "capillary" mean pressure in mm.Hg.
CO = Cardiac output in cc. per second.
1.332 = Conversion factor from mm.Hg. to dynes per cm.^{2}
CI = Cardiac Index in liters/min./m^2 B.S.A.
B.S.A. = Body Surface Area.

Material and Manner of Study

The subjects consisted of five male patients with pulmonary tuberculosis, all of whom had been hospitalized continuously for at least one year. Table I outlines the clinical and physical characteristics of the five pa-

TABLE I: CLINICAL CHARACTERISTICS OF FIVE PATIENTS WITH PNEUMOPERITONEUM FOR PULMONARY TUBERCULOSIS

Patient	Sex	Age Yrs.	Extent of Disease	Mos. in Hospital	Mos. of PNP	Wt., Lbs.	Ht., In.	B.S.A. M2	Hb Gm. Pct.	PCV Pct.	Comments
K.C.	M	31	Moderately Advanced. Upper 1/3 Bilateral	21	17	175	73	1.94	15.0	46	None
T.B.	M	34	Far Advanced. Upper 2/3 Left	24	23	129	65	1.63	15.8	51	Left Thoracoplasty; 16 mos.
W.M.	M	27	Far Advanced. Upper 1/3 Bilateral	24	24	135	69	1.73	14.4	47	None
W.J.	M	39	Far Advanced. Upper 1/3 Bilateral	33	31	149	70	1.85	15.0	47	Right Thoracoplasty; 29 mos.
O.W.	M	61	Far Advanced. Upper 2/3 Left	19	15	164	67	1.85	14.0	48	None

Abbreviations:

Pnp = Pneumoperitoneum.

Hb = Hemoglobin.

B.S.A. = Body Surface Area.

PVC = Packed cell volume or "hematocrit".

tients. Of particular note is the fact that patient T.B. had a left six-rib thoracoplasty 16 months previously and W.J. a seven-rib removal 29 months prior to this study. None of the patients had phrenic nerve paralysis at any time. All five were considered "apparently arrested" and had been on a regimen of progressive ambulation for at least two months prior to this study.

In four of the five patients refills were suspended until only a minimal amount of air remained, at which time the abdomen was soft and flat. At that time maximum breathing capacity, dead space, and lung volumes were determined. On the following day with the patient under basal conditions, cardiac catheterization was done with measurements of pressures, respiratory and arterial blood gases and cardiac output as indicated above. Then with a continuous recording of either pulmonary artery or pulmonary "capillary" pressure or both, the pneumoperitoneum was refilled to the patient's usual intraperitoneal pressure. After 15 to 30 minutes, pressures and cardiac outputs again were measured, and on the following day lung volume, dead space, and maximum breathing capacities were determined.

In one patient (O.W.) where discontinuance of pneumoperitoneum had been planned previously, two separate complete studies were done, the first with a full pneumoperitoneum and the second approximately one month after complete resorption of the air.

Results

The values for total lung volumes and subdivisions, and for the physiological dead space are shown in Table II and with the chief changes illustrated graphically in Figure 1. In all five patients there was a decrease

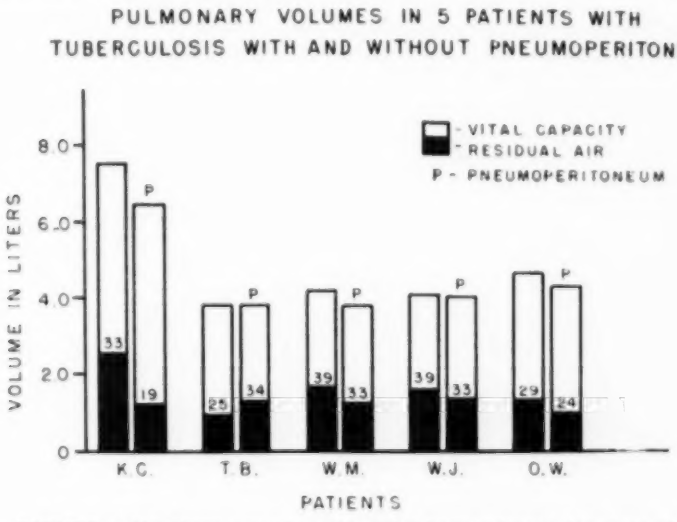

FIGURE 1: Numbers just above the solid bars indicate the ratio of the residual air to the total capacity (RA/TC × 100).

TABLE II: LUNG VOLUME AND SUBDIVISIONS
WITHOUT AND WITH PNEUMOPERITONEUM

Five Patients with Pulmonary Tuberculosis

	K.C.		T.B.		W.M.		W.J.		O.W.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
Tidal Volume cc.	478	458	538	582	628	591	473	457	458	492
Inspiratory Capacity, Liters	4.40	4.50	2.24	2.48	2.14	2.24	1.62	2.41	3.14	2.87
Expiratory Reserve, Liters	.70	.72	.38	.04	.42	.40	.53	.32	.21	.44
Vital Capacity, Liters	5.10	5.22	2.62	2.52	2.56	2.54	2.54	2.73	3.35	3.31
Per cent of Predicted	100	103	59	56	53	55	52	56	73	72
Residual Air, Liters	2.46	1.22	.94	1.31	1.66	1.66	1.61	1.33	1.35	1.02
Total Capacity, Liters	7.56	6.44	3.84	3.83	4.22	3.92	4.15	4.06	4.70	4.33
Per cent of Predicted	120	103	68	68	70	66	66	64	71	66
RA/TC × 100	33	19	25	34	39	33	39	33	29	24
Physiological Dead Space, cc.	—	—	—	—	121	123	268	201	299	261

in total capacity though in most cases this was slight. In four the residual air showed a greater decrease so that RA/TC × 100 fell to more nearly normal levels. The vital capacity changed but slightly, increasing in three patients (maximum 8 per cent) and decreasing in two patients (maximum 6 per cent) with a mean increase of 2 per cent for the group. The physiological dead space where measured, either decreased or was unchanged after pneumoperitoneum.

The ventilatory data are shown in Table III and illustrated graphically in Figure 2. In four there was a moderate decrease in maximum breathing capacity. The large increase after pneumoperitoneum in K.C. is without apparent reason. However, since this patient had carried pneumoperitoneum continuously for 17 months, the possibility exists that in the single month of gradual resorption of air, the diaphragm and muscles of the thoracic cage may not have regained adequate tone for the patient to show a maximum hyperventilation response.

The resting minute ventilation increased in three patients and fell in two, the respiratory rate being unchanged except in the case of O.W., whose tachypnea at the time of the control observation could be explained on the basis of anxiety and excitement.

The ratio of oxygen removal (cc. of oxygen consumed per liter of air ventilated) showed only the expected changes, a fall accompanying an increased minute volume and a rise with decreased ventilation. The changes in air velocity index paralleled those of the maximum breathing capacity.

The arterial oxygen saturation (Table IV) changed only minimally with

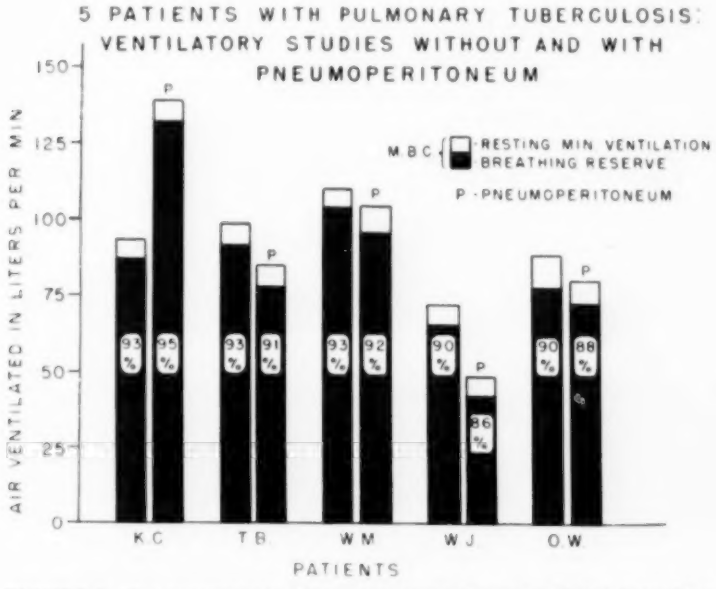

FIGURE 2: The percentages shown represent the ratio of the breathing reserve to the maximum breathing capacity (BR/MBC × 100).

TABLE III: VENTILATORY STUDIES
WITHOUT AND WITH PNEUMOPERITONEUM

Five Patients with Pulmonary Tuberculosis

	K.C.		T.B.		W.M.		W.J.		O.W.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
Resting Minute Ventilation l./min.	6.46	6.84	6.69	7.28	7.54	8.65	7.09	6.62	10.99	8.36
Respiratory Rate/min.	14	15	12	12	12	14	15	14	25	17
Maximum Breathing Capacity l./min.	93.5	139.1	98.8	85.4	111.5	104.7	72.6	49.1	88.7	81.1
Per cent of Predicted	68	102	88	76	89	84	60	40	88	80
Breathing Reserve l./min.	87.0	132.2	92.1	78.1	104.0	96.0	65.5	42.5	77	72
BR/MBC × 100	93	95	93	91	93	92	90	86	88	89
Oxygen Removal Ratio cc. O_2/liter ventilated	40.4	37.3	35.9	32.2	32.4	29.0	37.3	38.3	26.1	29.2
Air Velocity Index: Per cent Predicted MBC/Per cent Predicted V.C.	.68	.99	1.7	1.4	1.7	1.5	1.2	.71	1.2	1.1

TABLE IV: RESPIRATORY GASES IN THE ARTERIAL BLOOD
WITHOUT AND WITH PNEUMOPERITONEUM

Five Patients with Pulmonary Tuberculosis

	K.C.		T.B.		W.M.		W.J.		O.W.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
O_2 Capacity Volume Per cent	21.43	21.43	22.77	22.77	21.30	21.30	23.60	23.60	20.56	20.00
O_2 Saturation Resting Per cent	92.5	93.00	91.4	91.0	95.8	95.0	94.9	94.4	89.0	90.5
CO_2 Content Resting Volume Per cent	48.14	48.02	45.1	43.78	40.76	39.10	45.79	45.71	41.66	—
CO_2 Tension Resting, mm.Hg.	(41)*	(41)*	(39)*	35	34	41	41	(36)*		

* Figures in parentheses are calculated from nomogram with an assumed pH of 7.41.

pneumoperitoneum with no constant direction. The carbon dioxide content showed small but consistent decreases with pneumoperitoneum, all of which remained within the normal range.

The hemodynamic changes without and with pneumoperitoneum are outlined in Table V. Oxygen consumption varied little except in O.W., in whom the slightly high value in the control study reflects the anxiety mentioned above. The cardiac output showed small decreases in four patients and was unchanged in one (W.M.).

No consistent or striking changes were noted in the heart rate, arterial blood pressure, pulmonary artery, pulmonary "capillary" or right heart pressures. The changes in cardiac index and pulmonary artery pressure are illustrated in Figure 3. In one (T.B.), pressures in the iliac veins, the mid-abdominal portion, and the supra-diaphragmatic portion of the inferior vena cava were completely unchanged after a rather large pneumoperitoneum refill. The slight changes in total peripheral, total pulmonary, and pulmonary arteriolar resistance paralleled the changes in cardiac output since the pressures remained essentially unchanged. The initially elevated values for the total pulmonary and pulmonary arteriolar resistance in W.M. and O.W. probably reflect some degree of obliteration of the pulmonary vascular bed from the fibrous residues of the tuberculous process.

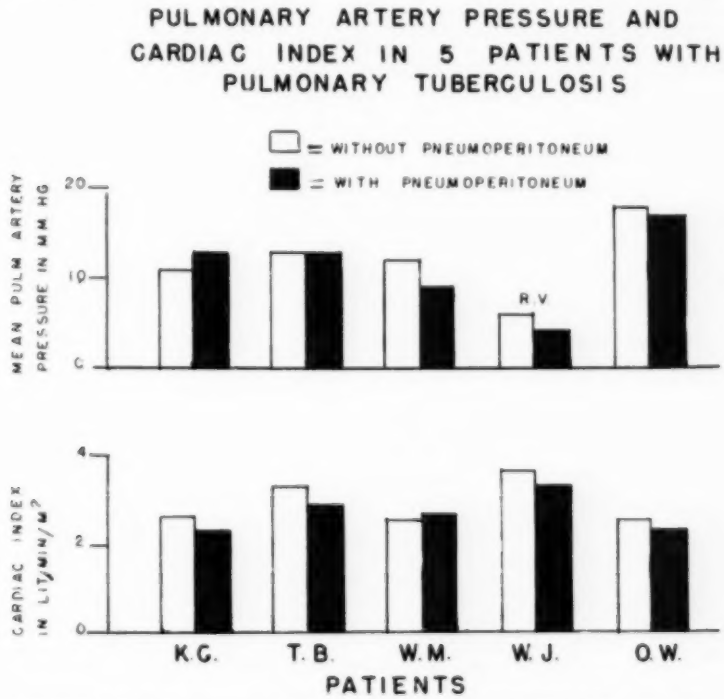

FIGURE 3: R.V. = mean right ventricular pressure in mm Hg. In this patient pulmonary artery pressures were not measured.

TABLE V: CARDIAC FUNCTION WITHOUT AND WITH PNEUMOPERITONEUM
Five Patients with Pulmonary Tuberculosis

	K.C.		T.B.		W.M.		W.J.		O.W.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
O_2 Consumption per min./m^2 BSA	116	114	132	128	118	119	122	116	132	114
Cardiac Output liters/min.	5.13	4.60	5.41	4.70	4.43	4.50	3.83	3.68	4.75	4.32
Cardiac Index l./min./m^2 BSA	2.64	2.37	3.32	2.88	2.56	2.60	2.07	1.99	2.57	2.34
Heart Rate/min.	66	68	71	69	78	86	76	78	91	91
Stroke Index cc./beat/m^2 BSA	40	35	47	42	33	30	27	26	28	26
Blood Pressures*										
Periph. Art.: Syst.	110	110	120	120	108	110	125	125	110	107
Diast.	75	80	80	80	70	60	95	95	70	68
Mean	87	90	93	93	83	78	105	105	83	81
Pulmon. Art.: Syst.	20	22	23	23	19	16	—	—	32	30
Diast.	7	8	8	8	8	6	—	—	11	11
Mean	11	13	13	13	12	9	—	—	18	17
Pulmon. "Capillary" Mean	6	6	7	8	5	4	—	—	5	7
Right Ventric.: Syst.	21	20	—	22	—	15	22	18	29	29
Diast. (end)	4	4	—	3	—	2	−1	−3	1	2
Mean	10	10	—	9	—	6	6	4	10	11
Right Auricle, Mean	4	4	5	7	2	2	0	0	−1	0
Superior Vena Cava	4	4	5	7	2	2	—	—	0	1
Resistances†										
Total Periph. Resistance	1,355	1,564	1,300	1,462	1,497	1,385	2,191	2,280	1,464	1,498
Total Pulmon. Resistance	171	226	192	221	371	276	—	—	303	314
Pulmon. Arteriolar Resistance	78	127	89	85	126	85	—	—	219	185
Heart Work										
KgM/min./m^2: Left Ventric.	3.11	2.89	4.00	3.64	2.87	2.72	2.97	2.86	2.88	2.72
Right Ventric.	.27	.31	.38	.25	.44	.34	.36	.31	.63	.57

* All Blood Pressures are expressed in mm.Hg.
† All Resistances are expressed in dynes seconds cm.$^{-5}$

Such obliteration has been postulated in healed miliary tuberculosis in a recent report.[26] Calculations of left and right ventricular work against pressure indicate slight but consistent decreases after pneumoperitoneum but these values all are well within the normal range.

Discussion

The earlier reports[5,13,11,4] that pneumoperitoneum causes a moderate reduction in vital capacity have not been confirmed by more recent investigations[15,16] or by the present study. The decrease in residual air accounts for the major portion of the fall in total capacity with no appreciable change in vital capacity. The slight reduction in maximum breathing capacity with pneumoperitoneum agrees with previous observations.[15,16] No significant changes in arterial oxygen saturation followed pneumoperitoneum, the arterial carbon dioxide content showing consistent but tiny decreases.

Arterial gas studies provided no evidence of impairment of respiratory function by this procedure.

Pneumoperitoneum in therapy of pulmonary tuberculosis appears to exert little or no effect on cardiac or circulatory function, no change being observed in arterial, right heart, or pulmonary artery pressures. The consistent though minimal fall in cardiac output is without apparent reason. It is of interest, however, that in a study of pneumoperitoneum in pulmonary emphysema,[17] all five patients exhibited decreases in cardiac output.

SUMMARY

1) The effect of pneumoperitoneum on cardiopulmonary function was studied in five patients with pulmonary tuberculosis.

2) Pneumoperitoneum caused a decrease in total lung volume primarily by virtue of a reduction in residual air with little or no change in vital capacity.

3) The maximum breathing capacity decreased slightly with pneumoperitoneum; the resting minute ventilation, respiratory rate and tidal volume showing no consistent changes.

4) The arterial oxygen saturation and arterial carbon dioxide content were unaffected by pneumoperitoneum.

5) Arterial, pulmonary arterial, pulmonary "capillary," right ventricular, right auricular, and vena cava pressures were unaffected by pneumoperitoneum.

6) Cardiac output showed a consistent though slight and statistically insignificant decrease with pneumoperitoneum.

RESUMEN

1) El efecto del neumoperitoneo en la función cardio-pulmonar fué estudiado en cinco pacientes con tuberculosis pulmonar.

2) El neumoperitoneo causó una disminución del volumen total principalmente en virtud de una reducción en el aire residual con poco o ningún cambio en la capacidad vital.

3) La capacidad respiratoria máxima disminuyó ligeramente con el neumoperitoneo; la ventilación de descanso por minuto, la frecuencia respiratoria y el volumen tidal no mostraron cambios consistentes.

4) La saturación de oxigeno arterial y del contenido de bióxido de carbono arterial no fueron afectados por el neumoperitoneo.

5) Las presiones arterial, arterio-pulmonar, pulmocapilar, ventricular derecha y veno-cava no fueron afectadas por el neumoperitoneo.

6) El rendimiento cardiaco mostró una definida disminución aunque insignificante y sin importancia estadística con el neumoperitoneo.

RESUME

1) Les auteurs ont étudié l'effet du pneumopéritoine sur la fonction cardio-pulmonaire chez cinq malades atteints de tuberculose.

2) Le pneumopéritoine à déterminé une diminution du volume total pulmonaire, en créant une réduction de l'air résiduel, et une altération légère ou nulle de la capacité vitale.

3) La ventilation maximum a montré une diminution nette sous l'influence du pneumopéritoine; tandis que la ventilation minute au repos, le rythme respiratoire et le volume de l'air courant ne montraient aucune modification importante.

4) Le pneumopéritoine n'a nullement intéressé la saturation oxygénée artérielle, et le taux d'acide carbonique artériel.

5) Le pneumopéritoine n'a eu aucune action sur les pressions artérielles, sur la pression de l'artère pulmonaire, sur celles des capillaires pulmonaires, du ventricule droit, de l'oreillette droite, et de la veine cave.

6) Le pneumopéritoine a créé une diminution du débit cardiaque nette bien que légère et statistiquement insignifiante.

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Pulmonary Function and Circulatory Dynamics in Artificial Pneumoperitoneum*

II. Studies on Patients with Pneumoperitoneum as a Therapeutic Measure in Pulmonary Emphysema.

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Although pneumoperitoneum at present is most widely used as a form of collapse therapy in pulmonary tuberculosis, this procedure had been applied some years earlier in the treatment of chronic pulmonary emphysema. In 1924 Reich[1] reported on this procedure, considering 300 to 500 cc. the ideal amount of air. He found greatly improved diaphragmatic motion, increased tidal air and respiratory minute volume, higher capillary oxygen saturation and even a decrease in alveolar carbon dioxide. There was often striking clinical improvement with a decrease in dyspnea, cyanosis, and coughing, and a reduction in the frequency of asthmatic attacks. Reich attributed the beneficial effects to mechanical improvement in breathing, and, because in some patients improvement persisted after resorption of the air, he concluded that these patients had regained the proper use of the diaphragm. Piaggio-Blanco in 1937[2] noted the effectiveness of pneumoperitoneum in patients with chronic pulmonary emphysema in a purely clinical study. Other reports[3,4] suggested that pneumoperitoneum was effective in decreasing the frequency and severity of attacks in uncomplicated bronchial asthma.

In 1950 Gaensler and Carter[5,6] and Furman and Callaway[7] reinvestigated this procedure in emphysema. The former authors studied the effect of pneumoperitoneum on ventilatory function and pulmonary capacity in 13 patients with chronic pulmonary emphysema, 10 of whom were improved clinically by the procedure. The residual air was always reduced, averaging 26 per cent less while the inspiratory capacity increased in all cases, averaging 24 per cent more. The vital capacity increased in 10, although the total capacity was somewhat decreased in all patients. A 33 per cent mean increase in maximum breathing capacity was accompanied by a reduced breathing requirement at rest. With standard exercise the breathing reserve increased from 68.2 per cent of the maximum breathing capacity to 80.5 per cent after treatment. Oxygen consumption was unchanged, the ventilatory equivalent being reduced. Two patients showed increased arterial oxygen saturation and decreased carbon dioxide tension after pneumoperitoneum especially in relation to exercise. A third showed no change in blood gases. Fluoroscopy demonstrated a marked increase in diaphragmatic motion although the amount of intraperitoneal air was

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comparatively small. Good correlation was obtained between clinical improvement and laboratory evidence of improved pulmonary function. Furman and Callaway obtained clinical improvement, increased vital capacity and exercise tolerance with pneumoperitoneum in five of seven patients.

The present study was undertaken to evaluate the effect of pneumoperitoneum on cardiovascular dynamics as well as pulmonary function in patients with pulmonary emphysema. The previous study[8] of patients with pulmonary tuberculosis and more nearly normal cardiopulmonary function may, with limitations, be used for comparison. Despite many recent investigations[9-16] the physiological defects in pulmonary emphysema are only partially understood. Circulatory and respiratory responses to pneumoperitoneum in the individual patient might aid in understanding the abnormal respiratory mechanisms operative in pulmonary emphysema and possibly further clarify this disorder. Conversely, an adequate correlation between objective physiological responses and the apparent degree of clinical improvement might provide a better guide to selection of the patient likely to benefit therapeutically from this procedure.

Material and Methods

The methods used were the same as those employed in the preceeding investigation.[8] Five male patients with chronic pulmonary emphysema whose symptoms had persisted for at least one year were studied. The mean age was 58 years, with a range of 56 to 61. The chief clinical and physical characteristics are shown in Table I. Four of the five patients are considered severe, the fifth (M.W.) moderately severe. They were treated in the hospital with bronchodilators, expectorants, postural drainage, antibiotics and oxygen as needed for a period of one to three months, and all appeared to have reached a "therapeutic plateau" prior to this study. Pulmonary capacity, ventilatory studies, arterial gas measurements, intracardiac, pulmonary artery and "capillary" pressures, and cardiac output determinations were made. They were studied again one month or more after pneumoperitoneum was initiated. The single exception was E.B. in whom pneumoperitoneum had been started elsewhere six months previously as therapy for his emphysema. He had received regular refills throughout this period. The peritoneal air was allowed to resorb almost completely before the initial study was done. Then the pneumoperitoneum refill was given with the cardiac catheter in place, the intracardiac pressure measurements and output being determined both before and after the refill. Pulmonary function studies were repeated the following day.

In the one patient (J.B.) with secondary polycythemia, the hemoglobin and hematocrit were brought to normal levels by repeated phlebotomy prior to the first study. The "before" and "after" packed cell volumes were held within the same range.

Results

The measurements of pulmonary capacity are presented in Table II and illustrated graphically in Figure 1. In the three patients, J.P., J.B. and

TABLE I: CLINICAL CHARACTERISTICS OF FIVE PATIENTS WITH PNEUMOPERITONEUM FOR PULMONARY EMPHYSEMA

Patient	Sex	Age	Diagnosis	Duration of Symptoms	Wt. Lbs.	Ht. Inches	B.S.A. M2	Hb Gm Pct.	PCV Pct.	Clinical Response to Pneumoperitoneum
J.P.	M	61	Chronic Pulmonary Emphysema, severe; Chronic Bronchitis and Asthma	5 years	130	66	1.64	15.0	49	Striking improvement
J.B.	M	56	Chronic Pulmonary Emphysema, severe; Cor. pulmonale Secondary Polycythemia	$1\frac{1}{2}$ years	115	70	1.63	13.5	49	Striking improvement
M.W.	M	58	Chronic Pulmonary Emphysema, moderately severe	1 year	148	72	1.88	14.5	45	Moderate improvement
C.C.	M	58	Chronic Pulmonary Emphysema, severe; Lymphoepithelioma of Nasopharynx	3 years	116	70	1.66	15.8	50	Unimproved
E.B.	M	61	Chronic Pulmonary Emphysema, severe; Psychoneurosis-Passive Dependency Reaction	7 years	114	68	1.62	15.0	44	Unimproved

Abbreviations:

Pnp = Pneumoperitoneum.

Hb = Hemoglobin.

B.S.A. = Body Surface Area.

PVC = Packed cell volume or "hematocrit".

M.W., who obtained definite clinical improvement there was an increase in inspiratory capacity of 21 per cent, 68 per cent and 19 per cent, respectively. By contrast, the two unimproved patients, C.C. and E.B., showed minimal decreases in inspiratory capacity. In like manner there was a reduction in residual air, total capacity, and the ratio of residual air to total capacity although the changes in M.W. were small. Those who were not improved showed increases in both residual air and total capacity, with a slight rise in the ratio of residual air to total capacity. The tidal volume increase in four but only appreciably so in J.P. and J.B. The increase in physiological dead space in four of the five patients is unexplained.

Table III outlines the results of the ventilatory studies, Figure 2 representing the principal findings graphically. The changes in resting minute ventilation were small and inconstant except in the case of M.W. whose initially high resting minute ventilation decreased 16 per cent after pneumoperitoneum. The only striking change in respiratory rate was that of J.B. whose fall in respiratory rate from 19 to 12 was balanced by a proportional increase in tidal volume. The maximum breathing capacity increased 47 per cent, 61 per cent and 21 per cent, respectively, in the three clinically improved patients with decreases of 27 per cent and 21 per cent in the two who were not helped.

The breathing reserve-maximum breathing capacity ratio showed similar changes. The oxygen removal ratio was initially low in all patients but changes with pneumoperitoneum were small and inconsistent. The air velocity index showed a fall from .95 to .63 in the case of J.B., the one who

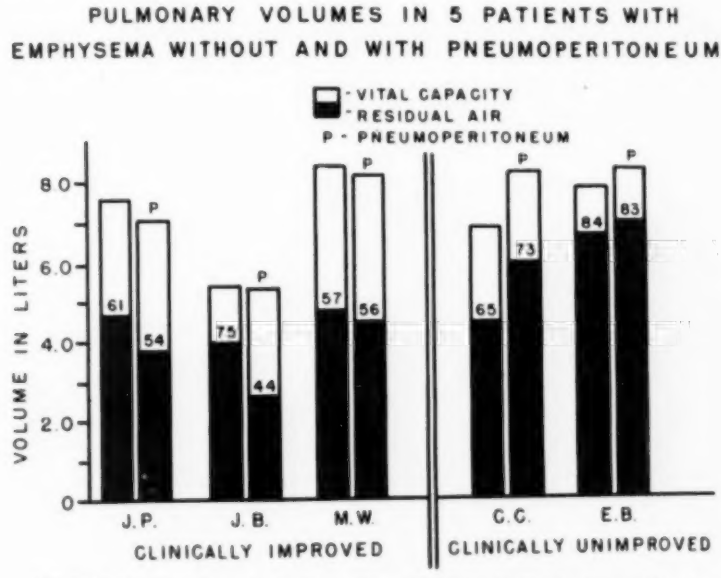

FIGURE 1: Numbers just above the solid bars indicate the ratio of residual air to the total capacity (RA/TC × 100).

TABLE II: LUNG VOLUME AND SUBDIVISIONS BEFORE AND AFTER PNEUMOPERITONEUM
Five Patients with Pulmonary Emphysema

	J.P.		J.B.		M.W.		C.C.		E.B.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
Tidal Volume cc.	545	599	384	600	501	511	342	332	452	466
Inspiratory Capacity, Liters	1.90	2.30	1.25	2.10	2.62	3.12	1.70	1.64	1.26	1.20
Expiratory Reserve, Liters	1.10	0.95	0.31	1.25	1.05	0.55	0.60	0.62	0.20	0.20
Vital Capacity, Liters	3.00	3.25	1.41	2.73	3.67	3.67	2.30	2.26	1.46	1.40
Per cent of Predicted	66	72	29	57	74	74	48	47	31	30
Residual Air, Liters	4.66	3.85	4.05	2.68	4.85	4.58	4.53	5.96	6.73	7.11
Total Capacity, Liters	7.66	7.10	5.46	5.41	8.52	8.25	6.83	8.22	8.19	8.51
Per cent of Predicted	117	108	79	78	120	116	98	120	121	125
RA/TC × 100	61	54	75	44	57	56	65	73	82	84
Physiological Dead Space, cc.	220	270	303	357	268	298	140	161	244	221

TABLE III: VENTILATION STUDIES BEFORE AND AFTER PNEUMOPERITONEUM
Five Patients with Pulmonary Emphysema

	J.P.		J.B.		M.W.		C.C.		E.B.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
Resting Minute Ventilation l./min.	6.25	6.77	7.29	7.21	10.00	8.37	7.87	7.64	9.70	9.33
Respiratory Rate/min.	12	11	19	12	20	17	23	23	21	20
Maximum Breathing Capacity Liters/min.	23.0	33.7	26.0	42.0	47.7	57.6	18.6	13.6	29.7	23.6
Per cent of Predicted	25	38	26.5	44.5	45	54	20	17	34	27
Breathing Reserve Liters/min.	16.8	26.9	18.7	34.8	37.7	49.2	10.7	6.0	20.0	13.3
BR/MBC × 100	73	80	72	83	79	86	58	44	67	56
Oxygen Removal Ratio cc. O_2/l. ventilated	33.8	33.6	31.6	30.5	26.5	27.5	28.7	28.2	25.7	24.0
Air Velocity Index: Per cent Predicted MBC/Per cent Predicted V.C.	.38	.53	.95	.63	.61	.73	.42	.36	1.08	.90

showed the greatest improvement. This inconsistency suggests that the initial VC was erroneously low. The initial air velocity index of 1.08 is an unusual finding in E.B. and not consistent with the reported data on patients with emphysema.[17] This will be discussed later in more detail.

The arterial blood oxygen and carbon dioxide changes are shown in Table IV. The decrease in oxygen capacity in J.B. reflects the lowering of hemoglobin concentration incident to phlebotomy.

The arterial oxygen saturation at rest increased to some degree in all except M.W. in whom there was a definite rise from 88.6 to 93.2 per cent with exercise after pneumoperitoneum. Arterial carbon dioxide content and tension fell appreciably in the three who showed improvement. The most striking response was that of J.B. who initially exhibited only 71 per cent arterial oxygen saturation at rest with carbon dioxide content and tension in the arterial blood of 66 volumes per cent and 67 mm. Hg, respectively. After 30 minutes of 100 per cent oxygen breathing, the oxygen saturation had only reached 85.7 per cent, the carbon dioxide content rising to 69 volumes per cent. He was too dyspneic and weak at this time to tolerate exercise. Following pneumoperitoneum the arterial oxygen saturation rose to 81 per cent with a fall in arterial carbon dioxide to 58 volumes per cent and a tension of 53 mm. of Hg. Even with exercise he maintained an oxygen saturation of 82.7 per cent with no change in carbon dioxide. Of particular note are the blood gas findings in E.B., who maintained normal arterial oxygen and carbon dioxide levels, despite a vital capacity 31 per cent and 34 per cent of predicted values before and after pneumoperitoneum, and despite the extremely large ratio of residual air to total capacity (82 per cent). Because of these unusual findings arterial blood gas

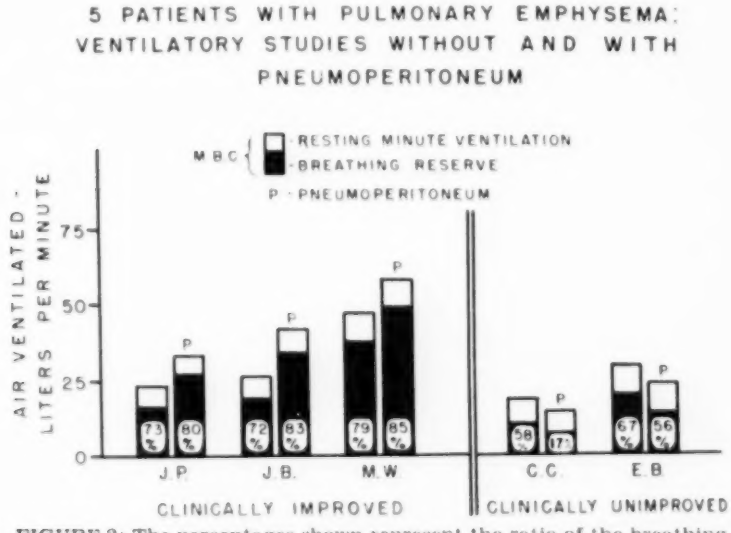

FIGURE 2: The percentages shown represent the ratio of the breathing reserve to the maximum breathing capacity (BR/MBC × 100).

TABLE IV: RESPIRATORY GASES IN THE ARTERIAL BLOOD BEFORE AND AFTER PNEUMOPERITONEUM

Five Patients with Pulmonary Emphysema

	J.P.		J.B.		M.W.		C.C.		E.B.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
O_2 Capacity, Volume Per cent	19.94	20.63	21.16	16.24	18.45	18.88	20.48	21.29	20.05	20.05
O_2 Saturation Per cent Resting	89.1	92.8	71.4	81.4	89.0	88.6	84.8	86.8	94.8	96.8
After Bronchodilator	90.0	—	—	—	—	—	—	—	—	—
100 Per cent O_2 Breathing	—	—	85.7	—	—	—	—	—	—	—
After Exercise	—	—	—	82.7	—	93.2	85.1	88.6	—	*
CO_2 Content, Volume Per cent Resting	58.5	54.4	66.33	57.90	51.82	48.46	54.14	55.27	49.84	48.91
100 Per cent O_2 Breathing	—	—	69.22	—	—	—	—	—	—	—
After Exercise	—	—	—	58.12	—	48.77	—	—	—	*
Blood pH, Resting	7.39	7.41	7.32	7.39	(7.41)	(7.41)	7.38	7.39	(7.41)	(7.41)
CO_2 Tension mm.Hg. Resting	52	46	67	53	(45)	(41)	49	48	(43)	(41)

* See text. Figures in parentheses are assumed normal pH or based on an assumed normal pH.

studies were repeated on this patient five days later at which time the maximum breathing capacity had not materially changed. At the time of this second study the resting arterial oxygen saturation was 91.4 per cent with a carbon dioxide content of 52.95 volumes per cent. With the arterial needle in place, the patient was exercised by walking over the two-step platform. After 12 trips over this platform in approximately two minutes, the dyspnea became so severe that he sat down gasping, unable to speak because of shortness of breath. An arterial blood sample, however, drawn within one minute after the termination of the exercise showed an oxygen saturation of 93 per cent, a rise of 1.6 per cent from the resting value, a carbon dioxide content of 51.40 volumes per cent, a fall of 1.55 volumes per cent. Six months previously the arterial oxygen saturation in another laboratory was 92 per cent, despite the same degree of apparent pulmonary insufficiency. This discrepancy between the pulmonary capacity-ventilatory studies and the blood gas levels will be discussed below.

The results of the cardiovascular function studies are depicted in Table V and Figure 3. Oxygen consumption in general showed decrease following pneumoperitoneum, which may be explained by lessening of anxiety and in some cases by a decrease in the muscular effort of breathing where dyspnea had been relieved. Initially, the cardiac output figures were normal except in the case of J.B. who had cor pulmonale and a high output (cardiac index 4.26 liters/min./M^2 BSA), and E.B. whose cardiac index was quite low (1.78 liters/min./M^2 BSA), although there was no clinical or physiological evidence of congestive heart failure. The cardiac output decreased in all five cases following pneumoperitoneum with a mean fall

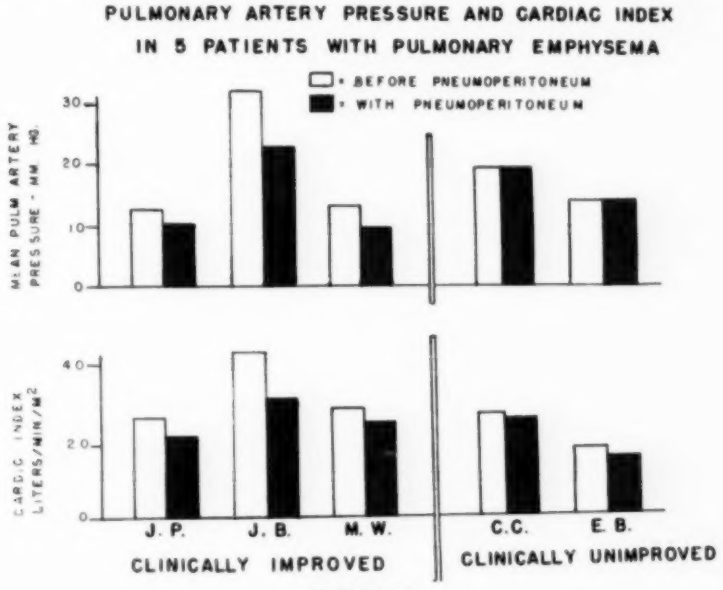

FIGURE 3

TABLE V: CARDIAC FUNCTION
BEFORE AND AFTER PNEUMOPERITONEUM
Five Patients with Pulmonary Emphysema

	J.F.		J.B.		M.W.		C.C.		E.B.	
	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.	Control	Pnp.
O_2 Consumption per min./m^2 BSA	112	124	122	117	123	104	117	112	142	126
Cardiac Output liters/min.	4.46	3.43	7.06	4.92	5.26	4.69	4.29	3.85	2.88	2.49
Cardiac Index l./min./m^2 BSA	2.66	2.07	4.26	3.07	2.80	2.49	2.57	2.35	1.78	1.54
Heart Rate/min.	82	65	74	68	76	72	82	82	105	105
Stroke Index cc./beat/m^2 BSA	32	32	58	45	37	35	31	28	16	14
Blood Pressures*										
Brach. Art.: Syst.	145	144	98	105	95	95	115	119	130	130
Diast.	80	66	58	60	60	60	75	70	86	86
Mean	102	95	71	75	72	72	88	86	100	100
Pulmon. Art.: Syst.	22	21	58	40	23	19	32	34	23	23
Diast.	9	5	19	14	8	4	12	12	9	10
Mean	13	10	32	23	13	9	19	19	14	14
Pulmon. "Capillary" Mean	—	8	9	9	2	0	8	7	6	6
Right Ventric.: Syst.	23	24	45	28	25	20	35	25	24	19
Diast. (end)	−1	−2	2	3	3	1	0	−2	4	0
Mean	7	7	17	11	10	8	12	7	11	6
Right Auricle, Mean	2	0	−2	2	0	1	0	0	4	4
Resistances†										
Total Periph. Resistance	1,828	2,214	804	1,218	1,109	1,210	1,639	1,785	2,776	3,211
Total Pulmon. Resistance	233	233	363	374	198	153	354	395	389	449
Pulmon. Arteriolar Resistance	—	47	260	228	167	153	205	249	222	257
Heart Work										
KgM/min./m^2: Left Ventric.	3.70	2.67	4.04	3.08	2.73	2.39	2.99	2.73	2.43	2.10
Right Ventric.	0.42	0.24	1.83	0.92	0.52	0.29	0.70	0.71	0.26	0.22

* All blood pressures are expressed in mm.Hg.
† All resistances are expressed in dynes seconds cm.$^{-5}$

of 18 per cent and a range of 10 to 30 per cent. The arterial blood pressures were unchanged. The initial pulmonary artery pressure was elevated only in J.B., the patient with cor pulmonale, and after pneumoperitoneum there was a fall in pressure from 58/19 to 40/14. Although initial pulmonary artery pressures were normal in the other four, the two (J.P. and M.W.) who improved clinically following pneumoperitoneum had definite pressure falls in contrast to the other two whose pressures were unchanged. The pulmonary "capillary" pressure, right ventricular and right auricular pressures showed no remarkable changes. All five showed increased total peripheral resistance after pneumoperitoneum, a reflection primarily of the fall in cardiac output. The changes in total pulmonary and pulmonary arteriolar resistances were inconsistent. The work of the left ventricle against pressure, although within normal limits initially, fell in all cases after pneumoperitoneum, the degree of fall being much greater in three patients who were benefited by the procedure. The work of the right heart against pressure was initially elevated only in J.B. but decreased following pneumoperitoneum below the upper limit of normal.

Discussion

All five of the patients exhibited increased diaphragmatic motion on fluoroscopy with a 2 to 6 cm. excursion from expiration to inspiration. There was no correlation between diaphragmatic excursion and clinical or physiologic improvement.

Excellent correlation was obtained between clinical improvement and improvement in cardiopulmonary function. The increase in inspiratory capacity, together with the reduction in total capacity, residual air and RA/TC ratio, following pneumoperitoneum, is in complete agreement with previous observations.[5] It is of interest that patients with pulmonary tuberculosis and more nearly normal lung function, similarly studied,[8] showed lung volume changes in the same direction but smaller in amount. The two patients who were not improved showed little change or slight increase in residual air and RA/TC ratio, in addition to a reduced maximum breathing capacity. It is difficult to escape the conclusion that in these patients not only was pneumoperitoneum ineffective but possibly detrimental from the standpoint of pulmonary capacity and ventilation.

The pulmonary capacity and ventilatory measurements in E.B. seem incompatible with the blood gas figures. This 61 year old man showed classical pulmonary emphysema by both physical examination and x-ray film. The slightest exertion would bring on dyspnea. In support of these clinical findings was a total lung capacity of 121 to 125 per cent of the predicted value, the measurements being done on two occasions, each time with excellent duplicate checks. The ratio of residual air to total capacity was 82 to 84 per cent and the maximum breathing capacity was 34 per cent of the predicted value, yet not only did he demonstrate near normal resting arterial oxygen saturation and a normal carbon dioxide content but on exercise sufficient to cause severe dyspnea, the oxygen saturation actually increased, the carbon dioxide showing a decrease. Although the explana-

tion of these interesting findings is not readily apparent, it seems inescapable that the circulatory and diffusion mechanisms in this patient must be extremely efficient to maintain near normal blood gases in the face of such a severe ventilatory defect. In addition, the prompt appearance of dyspnea in this patient limits his activity to such an extent that his blood gases are protected.

E.B. also exhibits an air velocity index of 1.08, a perfectly normal value instead of the much lower index (.40 to .60) which is usually seen in emphysema.[17] Finally the low cardiac output in this patient (cardiac index 1.78 liters/min./M^2 BSA) also is without explanation, especially since there is no evidence of heart disease.

The elevation of pulmonary arterial pressure in chronic emphysema as in J.B. is explained in part by an organic reduction in the pulmonary vascular bed secondary to scarring and fibrosis. However, recent investigations[19,20] have indicated that hypoxia produces pulmonary artery vasoconstriction and another study[21] has implicated carbon dioxide retention as a cause of pulmonary hypertension. The fall in pulmonary artery pressure in J.B. after pneumoperitoneum might well be the result of the increase in arterial oxygen saturation and the decrease in carbon dioxide retention.

The fall in cardiac output in all five patients after pneumoperitoneum, coupled with decreased outputs in four of five similarly studied with pulmonary tuberculosis[8] while by no means conclusive, is sufficiently suggestive to warrant further investigation. The lowering of cardiac output secondary to improved oxygenation and reduction of carbon dioxide retention as in J.P. and J.B. is understandable, especially where there is a decrease in pulmonary hypertension and pulmonary resistance. However, a fall in cardiac output in the absence of clinical or physiological improvement is less easily understood. It is possible that pneumoperitoneum might exert pressure on the inferior vena cava or iliac veins with reduction in venous return.

In this connection pressure measurements in the superior vena cava and in both the abdominal and thoracic portions of the inferior vena cava were obtained in E.B. immediately before and immediately after pneumoperitoneum. The pressures were normal initially and did not change after pneumoperitoneum. This is in complete agreement with similar observations on a patient in the tuberculosis series. It is possible though unlikely that appreciable reduction in venous return would result from pneumoperitoneum in the absence of measurable pressure increase in the vena cava.

Pneumoperitoneum, when effective in therapy of pulmonary emphysema, has as its basic action increase in the range of motion of the diaphragm with a resulting improvement in ventilatory capacity and breathing reserve. The improvement observed in J.P., J.B., and M.W., in the absence of an increased minute volume suggests that with the reduction in residual air secondary to pneumoperitoneum a more efficient distribution of inspired air has occurred with an increase in "alveolar ventilation" and more efficient oxygen and carbon dioxide exchange.

The failure of C.C. and E.B. to improve is more difficult to explain, and

must await further study. Although the number reported in the literature thus far is too small to furnish a basis for the selection of patients, it is hoped that when more cases are reported, some type of rational approach may be applied to the use of pneumoperitoneum. It should be emphasized that the clinical improvement in some cases is dramatic, as in the case of J.B. who was chronically dyspneic at rest, but after pneumoperitoneum was able to breathe comfortably even with limited ambulation.

SUMMARY

1) Cardiopulmonary function was investigated in five patients with chronic pulmonary emphysema before and after therapeutic pneumoperitoneum.

2) Striking clinical improvement occurred in two and moderate improvement in one. Two showed no improvement.

3) Clinical improvement was associated with an increase in inspiratory capacity and maximum breathing capacity and a reduction in residual air, total pulmonary capacity and the ratio of residual air to total capacity. The arterial oxygen saturation increased with a concomitant reduction in carbon dioxide retention.

4) One patient with cor pulmonale and pulmonary hypertension demonstrated a sizable reduction in pulmonary artery pressure following pneumoperitoneum and attending improvement in blood gases.

5) The cardiac output decreased in all five cases following pneumoperitoneum, the percentage fall ranging from 10 to 30 per cent.

RESUMEN

1) La función cardiopulmonar fué investigada en cinco pacientes con emfisema pulmonar crónico antes y después del neumoperitoneo terapéutico.

2) Extraordinaria mejoría clínica tuvo lugar en dos y mejoría moderada en uno. Dos de ellos no mostraron progreso.

3) El progreso clínico iba acompañado de un aumento en la capacidad inspiratoria y máxima capacidad respiratoria y una reducción en el aire residual, capacidad pulmonar total y la relación de aire residual a capacidad total. La saturación de oxígeno arterial aumentó, con una reducción concomitante de la retención de bióxido de carbono.

4) Un paciente con cor pulmonale e hipertensión pulmonar mostró una reducción considerable en la presión artero pulmonar después del neumoperitoneo y resultó un mejoramiento en los gases sanguíneos.

5) El rendimiento cardiaco disminuyó en todos los cinco casos después del neumoperitoneo, siendo el porcentaje de disminución entre un 10 a 30 por ciento.

RESUME

1) Les auteurs ont étudié la fonction cardio-pulmonaire chez cinq malades atteints d'emphysème pulmonaire chronique, avant et après pneumopéritoine thérapeutique.

2) Ils constatèrent une amélioration clinique frappante dans deux cas, une amélioration modérée dans un cas, aucune amélioration dans les deux autres.

3) L'amélioration clinique était associée à un accroissement de la capacité

inspiratoire et de la ventilation maximum, et à une réduction de l'air résiduel, de la capacité pulmonaire totale, et du rapport de l'air résiduel et de la capacité totale. La saturation oxygénée artérielle augmenta avec une diminution concomittante de la rétention d'acide carbonique.

4) Chez un malade atteint de coeur pulmonaire et d'hypertension de la circulation pulmonaire, le pneumopéritoine entraina une réduction appréciable de la pression de l'artère pulmonaire. Il en résulta également une augmentation des gaz du sang.

5) Dans tous les cinq cas, le pneumopéritoine fut suivi d'une diminution du débit cardiaque atteignant un taux de 10 à 30%

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The Significance of Cell Types in Bronchogenic Carcinoma*

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Physicians dealing with diseases of the thorax have long been aware that carcinoma of the lung varies greatly in its clinical manifestations, and that certain types of bronchogenic carcinoma are much more amenable to surgical eradication than others. The great frequency with which bronchogenic carcinoma occurs and its apparent increasing incidence make it essential to determine as far as possible the various factors that may influence the course of the disease.

In discussing bronchogenic carcinoma, it is first essential to define what is included by the term. Bronchogenic carcinoma is a primary carcinoma of the lung which is presumed to originate in the mucosa of the bronchi. Metastatic carcinoma of the lung, adenoma of the bronchus, and alveolar cell tumor must be distinguished from bronchogenic carcinoma, for not only are their clinical course and prognosis different from those of bronchogenic carcinoma, but they have an entirely different source of origin.

The results of early studies that were carried out to classify carcinoma of the lung solely on the basis of grade of malignancy of the tumor according to the method of Broders were soon found to be of little or no clinical, surgical or prognostic value. It has long been recognized that true bronchogenic carcinoma may assume a variety of forms, and many terms have been utilized by pathologists to describe these various changes. This lack of uniformity in terminology has made an understanding of the significance of cell types in carcinoma of the lung difficult. It is only since sufficient surgical and necropsy material has become available that it is possible to study and correlate the clinical course of the disease with survival following operative intervention and to devise a workable histologic classification.

In order to study the problem of the significance of cell types of bronchogenic carcinoma, the records of 1,000 cases of proved carcinoma of the lung, taken at random from the files of the Mayo Clinic, were reviewed. In each case, the diagnosis of carcinoma of the lung was based on the examination of bronchoscopic specimens, specimens taken for biopsy at the time of thoracotomy for inoperable neoplasms, and surgical specimens obtained by lobectomy or pneumonectomy. This series did not include any case in which there was evidence of carcinoma elsewhere in the body or in which there was a chance that the pulmonary lesion might be metastatic.

*Read at the Joint Session of the First International Congress of Bronchoesophagology and the Second International Congress on Diseases of the Chest of the American College of Chest Physicians, Rio de Janeiro, Brazil, August 24 to 30, 1952.

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Of the 1,000 patients in the cases in this series, 895 were men and 105 were women. The ratio of males to females, therefore, was 8.5:1. The ages of the patients ranged from 22 to 80 years. Operation for the bronchogenic carcinoma was performed in 479 of the 1,000 cases.

Some bronchogenic carcinomas are not made up of a single cell type but have a mixed cellular pattern. Part of the tumor may be of one cell type and another part may be of a different type. In attempting to classify tumors of this kind, the dominant type of cell present in the available histologic material was selected, and the tumor was classified as of that type. The minor histologic pattern was disregarded.

TABLE I

CELL TYPE OF BRONCHOGENIC CARCINOMA IN 1,000 CASES

Cell Type	CASES	
	Number	Per cent
Small cell carcinoma	90	9.0
Adenocarcinoma	137	13.7
Large cell carcinoma	378	37.8
Squamous cell carcinoma	395	39.5
TOTAL	1,000	100.0

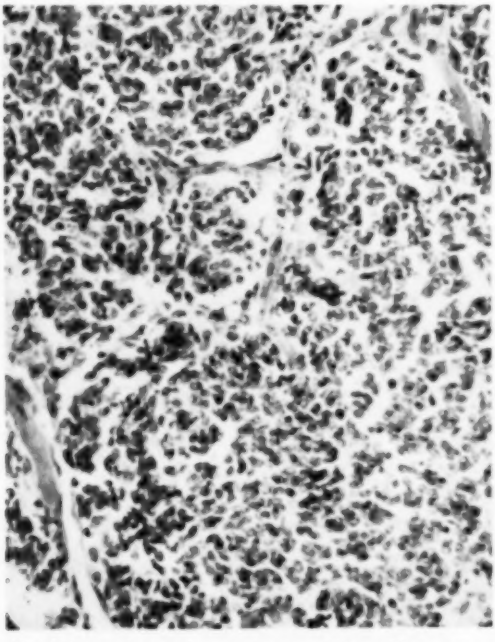

FIGURE 1: Small cell bronchogenic carcinoma. The cells are very small and are not forming glands. (Hematoxylin and eosin stain; x 200).

One of us (McDonald) and his associates[1-5] have divided bronchogenic carcinomas into four groups: (1) small cell carcinomas, (2) adenocarcinomas, (3) squamous cell carcinomas, and (4) large cell carcinomas.

Small Cell Carcinoma

A small cell carcinoma (Figure 1) is one in which the cells are small, with little cytoplasm surrounding the nucleus. The nucleus makes up almost 90 per cent of the cell. Nucleoli are not a prominent feature of this type of cell. This type of tumor is often designated as the "oat-cell type of cancer," "spindle-cell cancer," or "sarcoma."

The various types of bronchogenic carcinoma produce a gross picture which is more or less characteristic. In cases of small cell bronchogenic carcinoma, the involved bronchus is a large one, either the main stem bronchus or a primary division of the lobe bronchi (Figure 2). The lumen of the bronchus is stenotic, and the growth does not tend to produce a polypoid tumor mass in the bronchial lumen. The carcinoma extends beyond the involved bronchus to adjacent tissues. Oftentimes, the extrabronchial tumor mass is much larger than the part within the lung. In its most characteristic form, this type of bronchogenic carcinoma simulates a mediastinal tumor in the roentgenogram.

In 90, or 9 per cent, of the entire series of 1,000 cases the tumor was a small cell carcinoma (Table I). Although it was the least common of the bronchogenic carcinomas, it had the gravest prognosis. It is a disease that possesses a peculiar predilection for males. Eighty-seven of the patients were men and only three were women. The ratio of males to females, therefore, was 29:1. The average age of the patients was 46 years. The youngest patient was 36 years of age and the oldest was 75 years. All of the patients with small cell carcinoma had symptoms referable to the

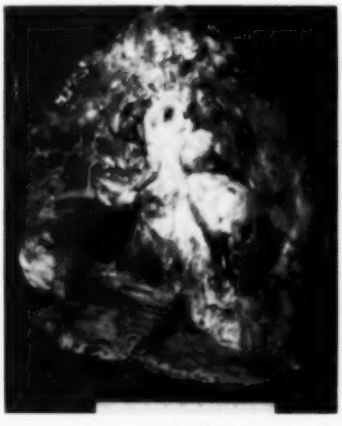

FIGURE 2

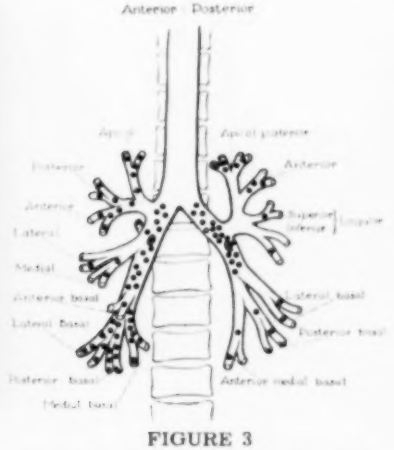

FIGURE 3

Figure 2: Small cell bronchogenic carcinoma. The tumor has produced a stenosis of the main bronchus, and there is evidence of peribronchial extension.—*Figure 3:* Distribution of small cell bronchogenic carcinomas in 84 cases.

thorax. Such symptoms were not present in all of the cases of the other types of carcinoma. The symptoms were indistinguishable from those of other types of bronchogenic cancer with the single exception that, on the average, the duration of symptoms before the diagnosis was established was of slightly shorter duration, being but 5.9 months. The sedimentation rate of the erythrocytes was not found to be of any value in distinguishing one type of bronchogenic carcinoma from another, and was elevated, on the average, in all types of carcinoma. In all of the 90 cases of small cell carcinoma, roentgenographic examination of the thorax disclosed changes which might be interpreted as indicative of a tumor.

The study of the gross surgical specimens revealed that most of the small cell carcinomas were of large size. With one exception, the tumor was situated either in the main stem or in a major secondary bronchus. If one divides the lung into two portions so that the primary and secondary bronchi are regarded as the central portion of the lung and the tertiary and distal bronchi are regarded as the peripheral portion, small cell carcinoma is essentially a tumor of the central portion of the lung.

In 84 of the 90 cases of small cell carcinoma, accurate information was available concerning the lobe of the lung involved. It was found that the lesion was on the right side in 51 cases and on the left side in 33 cases. The distribution according to lobe is shown in Figure 3. With almost all the small cell carcinomas arising from the central portion of the lung, one would anticipate being able to visualize the lesion bronchoscopically and to obtain tissue for microscopic examination in a high percentage of cases. This proved to be true. Bronchoscopy was performed in 81 of the 90 cases, and it disclosed a tumor in 67, or 82.7 per cent, of the 81 cases. In 62, or 76.5 per cent, of the 81 cases, microscopic examination of tissue which was removed by bronchoscopy revealed that the lesion was a carcinoma.

Cytologic examination of the sputum and bronchial secretions was found to be highly effective in the diagnosis of small cell bronchogenic carcinoma. It disclosed malignant cells in 93.5 per cent of the cases in which it was employed.

The tumor was considered operable in only 30 of the 90 cases. An exploratory operation was performed in 30 cases, but it was possible to remove the tumor in only 15 of these cases. Pneumonectomy was performed in all of these 15 cases. Study of the surgical specimens showed involvement of the hilar nodes in every case. Of the 15 patients who underwent pneumonectomy, only three were living two years after operation. One was living five years later. This would seem to indicate that the prognosis with respect to surgical eradication is extremely poor in cases of small cell carcinoma.

Adenocarcinoma

Adenocarcinoma (Figure 4) is characterized by cells which are forming glands or producing secretion. The diagnostic criterion is the presence of definite alveolar, acinar or papillary structures, or the formation of extracellular or intracellular mucus with columnar or cuboidal configuration of the cells.

Grossly, an adenocarcinoma of the lung is usually a peripheral tumor, oftentimes sharply circumscribed and situated subjacent to the pleura (Figure 5). In a small percentage of cases, a small bronchus can be traced into the tumor mass. In most cases, however, it is impossible to identify an involved bronchus intimately associated with the tumor.

In 137, 13.7 per cent, of the entire series of 1,000 cases of primary bronchogenic carcinoma, the tumor was an adenocarcinoma. Although adenocarcinoma occurs more frequently in men than in women, the predilection was not as great as in cases of the other types of bronchogenic carcinoma. One hundred and six of the patients were men and 31 were women. The ratio of males to females, therefore, was 3.4:1. The average age of the patients was 53 years. The youngest patient was 31 years of age and the oldest was 71 years. When the patients were divided into groups according to their ages by decades, those in the largest group were found to be in the sixth decade. The symptoms of adenocarcinoma were essentially the same as those of other types of bronchogenic carcinoma. However, in an occasional case, the patient was asymptomatic. The average duration of symptoms in the cases of adenocarcinoma was 7.9 months. Roentgenologic examination of the thorax disclosed evidence of an abnormality in all of the 137 cases.

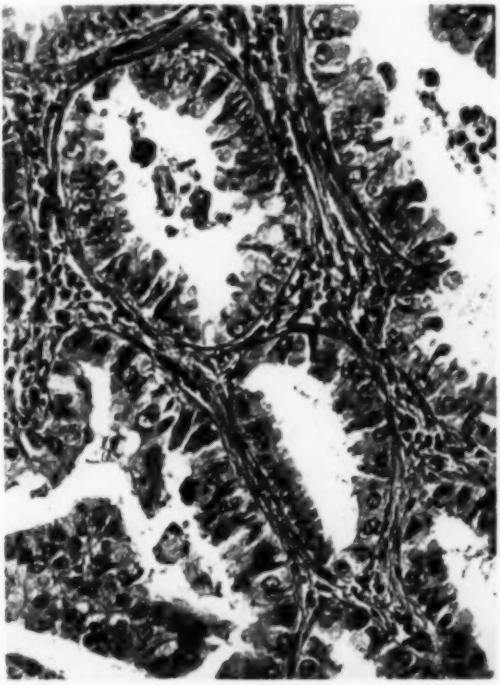

FIGURE 4: Bronchogenic carcinoma, adenocarcinoma type. The carcinoma cells are forming acini. (Hematoxylin and eosin stain; x 200).

Adequate surgical specimens were available for examination in 65 of the 137 cases. The distribution of the tumors in the 65 cases is shown in Figure 6. In 34 of the cases the tumor involved the right lung, and in 31 cases it was situated in the left lung. The tumor originated in the peripheral portion of the lung in 43 (66.2 per cent) of the 65 cases, and in the central portion of the lung in 22 cases (33.8 per cent).

In contrast to small cell carcinomas which are primarily central in origin, adenocarcinomas are almost twice as common in the peripheral portion of the lung. One, therefore, would not anticipate being able to visualize the lesion as frequently as small cell carcinoma on bronchoscopic examination. This indeed proved to be the case. Bronchoscopy was performed in 57 of the 137 cases, and it disclosed a tumor in only 22, 38.5 per cent, of the 57 cases. Microscopic examination of tissue removed by bronchoscopy, disclosed carcinoma in only 13 or 22.8 per cent of the cases in which bronchoscopy was performed.

Cytologic examination of sputum or bronchial secretions was performed in 82 of the 137 cases of adenocarcinoma. In 40 or 48.8 per cent of the 82 cases, it disclosed malignant cells.

Eighty-four of the patients were regarded as suitable candidates for exploratory thoracotomy. In 56 cases it was possible to resect the tumor. This figure in many respects is misleading as to the operability of adenocarcinoma. Because of the great strides that have been made in thoracic surgery, the percentage of cases of adenocarcinoma in which resection can be performed successfully is much higher today than it was 10 years ago. In the period from 1945 through 1949, an exploratory operation was performed in 68.7 per cent of the cases of adenocarcinomas observed at the Mayo Clinic, and resection was performed successfully in 70.9 per cent of cases in which exploratory thoracotomy was performed. The surgical prognosis

FIGURE 5

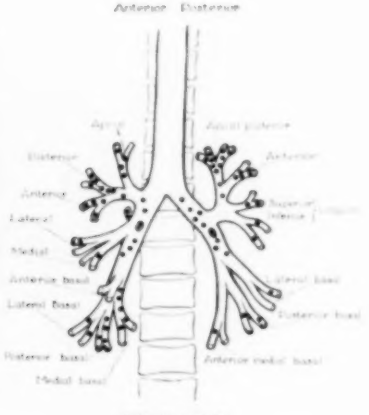

FIGURE 6

Figure 5: Bronchogenic carcinoma, adenocarcinoma type. The carcinoma is situated in the periphery of the lung. No connection with the bronchus could be found.
Figure 6: Distribution of adenocarcinomas in 65 cases.

in the cases of adenocarcinoma was somewhat better than it was in the cases of small cell carcinomas. At the end of two years, 33.3 per cent of the patients who had undergone resection of adenocarcinoma were living and well.

Squamous Cell Carcinoma

In a squamous cell carcinoma (Figure 7), at least some of the malignant cells show evidence of epidermoidization, usually, the production of keratinized or cornified material in at least some of the cells. The presence of prickle cells is accepted as sufficient evidence to classify a tumor as a squamous cell carcinoma.

Bronchogenic carcinoma of the squamous cell type is usually found in a large bronchus (Figure 8). Characteristically, it either produces a polypoid tumor mass projecting into the bronchus from the wall, or it produces a cicatricial narrowing of the bronchial lumen. There usually is not as much peribronchial extension as is seen in cases of small cell bronchogenic carcinoma. Cavitation is more commonly seen in cases of bronchogenic carcinoma than in cases of the other types of carcinoma.

Squamous cell carcinoma was the most frequent type of bronchogenic carcinoma in this series of 1,000 cases. In 395, or 39.5 per cent of the cases, the tumor was of the squamous cell variety. It was found to affect men predominantly, as 380 of the patients were men and only 15 women. The ratio of males to females, therefore, was 25.3:1. The average age of the patients was 52 years. When the patients were divided into groups according to their ages by decades, those in the largest group were found to be in the sixth decade. In only eight of the 395 cases were the patients less than 40 years of age, and only one was less than 30 years of age. The symptoms produced by squamous cell carcinoma were essentially the same as those observed in cases of the other types of bronchogenic carcinoma, and the average duration of symptoms before the diagnosis was established was six months. Roentgen examination of the thorax was highly informative, as it disclosed abnormal findings in 99 per cent of the 395 cases.

Exploratory thoracotomy was performed in 245 or 62 per cent of the 395 cases and resection was performed in 182 of the 245 cases. During the past five years, resection has been performed in 71 per cent of the cases in which the tumor was of the squamous cell type. Figure 9 shows the distribution of the tumors in the 182 cases in which resection was performed. The tumor was situated in the right lung in 96 or 52.7 per cent of the cases, and in the left lung in 86 or 47.3 per cent. Study of the surgical specimens showed that the tumors involved primarily the central portion of the lung, and in only four of the 182 cases was the tumor truly peripheral in situation in that it was more than 4 cm. from the main stem bronchus or its continuation as the lower lobe bronchus.

As one might anticipate from the site of most squamous cell carcinomas of the bronchial tree, bronchoscopy was highly effective in visualization of the lesions. Bronchoscopy was performed in 382 of the 395 cases, and it disclosed a lesion in 322 or 84.2 per cent of the 395 cases. In 306 or 80 per

cent of the 382 cases in which bronchoscopy was performed, biopsy disclosed that the lesion was a squamous cell carcinoma.

Cytologic examination of the sputum or bronchial secretions was performed in 221 of the 395 cases of squamous cell carcinoma. It disclosed carcinoma cells in 160 or 72.3 per cent of the 221 cases.

In 68 of the 182 cases in which resection was performed, the patients were traced for two years after the operation. Of the 68 patients in these

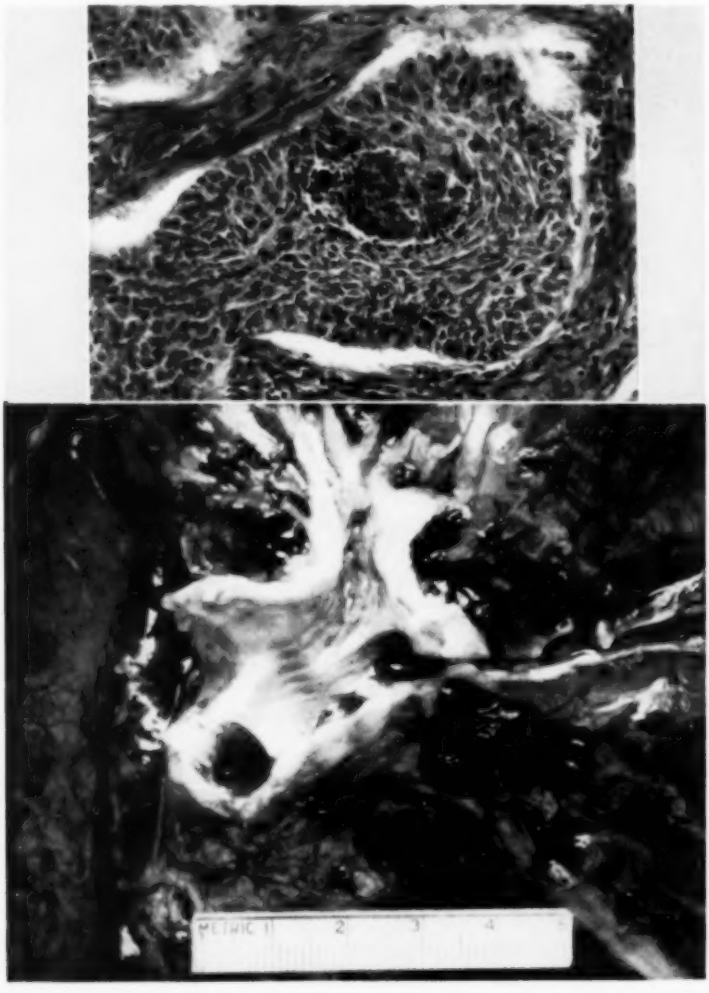

FIGURE 7 (top): Bronchogenic squamous carcinoma with definite evidence of squamatization. (Hematoxylin and eosin stain; x 200).—FIGURE 8 (bottom): Bronchogenic carcinoma, squamous type, involving the upper lobe bronchus. The carcinoma has produced narrowing of the bronchial lumen, but there is very little evidence of peribronchial extension, unlike a small cell carcinoma.

cases, 38 or 55.8 per cent were alive at the end of this period. Of 27 patients who were traced for five or more years after the operation, 14 or 51.9 per cent were alive when the last follow-up data were obtained. It should be pointed out that none of the patients who did not undergo operation were living at the end of three years. It is obvious, therefore, that squamous cell carcinoma is by far the most responsive to surgical eradication of all the types of bronchogenic carcinoma. It was found that those patients with involvement of the regional lymph nodes had less than half as good a chance of surviving five years following pulmonary resection as those without such involvement.

Large Cell Carcinoma

In a large cell carcinoma (Figure 10) the neoplastic cells do not show any evidence of epidermoidization, glandular formation, or the production of secretion. The cells are considerably larger than those seen in small cell carcinoma, and have more abundant cytoplasm. Large cell carcinoma in many respects represents a more or less negative diagnosis. There has been a tendency by many pathologists to group carcinomas of this type with those of the small cell type under the mysterious term, "undifferentiated carcinoma." Such a classification does not seem justified, since the clinical outlook in cases of large cell carcinoma is different from that in cases of small cell carcinoma.

The gross appearance of a large cell carcinoma is not as characteristic as that of other varieties of bronchogenic carcinoma. It becomes obvious that this might be expected when one realizes that some large cell carcinomas are, in reality, highly undifferentiated forms of squamous carcinoma, while others represent highly undifferentiated forms of adenocarcinoma.

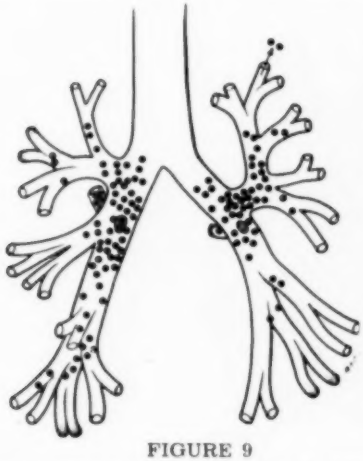

FIGURE 9

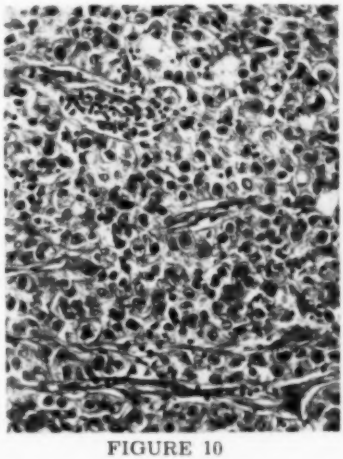

FIGURE 10

Figure 9: Distribution of squamous carcinomas in 121 cases in which resection was performed. — *Figure 10:* Bronchogenic carcinoma, large cell type. The cells are considerably larger than those of the small cell type. However, there is no evidence of glandular formation or squamatization. (Hematoxylin and eosin stain; x 200).

Some of these tumors are found in large bronchi and others are found near the periphery of the lung.

In 378 or 37.8 per cent of the entire series of 1,000 cases, the tumor was of the large cell type. Of the 378 patients, 322 were men and 56 were women. The ratio of males to females, therefore, was slightly less than 6:1. The ages of the patients ranged from 22 to 80 years, and the average age was 55 years. When the patients were divided into groups according to their ages by decades, those in the largest group were found to be in the sixth decade. The symptoms were essentially the same as those in cases of the other types of carcinoma, and the average duration of symptoms before diagnosis was made was the same as it was in the cases of adenocarcinoma. In more than half of the cases, the symptoms had been present for less than four months. In eight of the 378 cases, roentgenographic examination of the thorax did not reveal any abnormality.

In 130 of the 378 cases of large cell carcinoma, surgical specimens were examined in order to determine the site of origin of the tumor. In 75 or 57.7 per cent of the 130 cases, the tumor was situated in the central portion of the lung. In the remaining 55 cases (42.3 per cent), it was situated in the peripheral portion of the lung. Figure 11 shows the distribution of

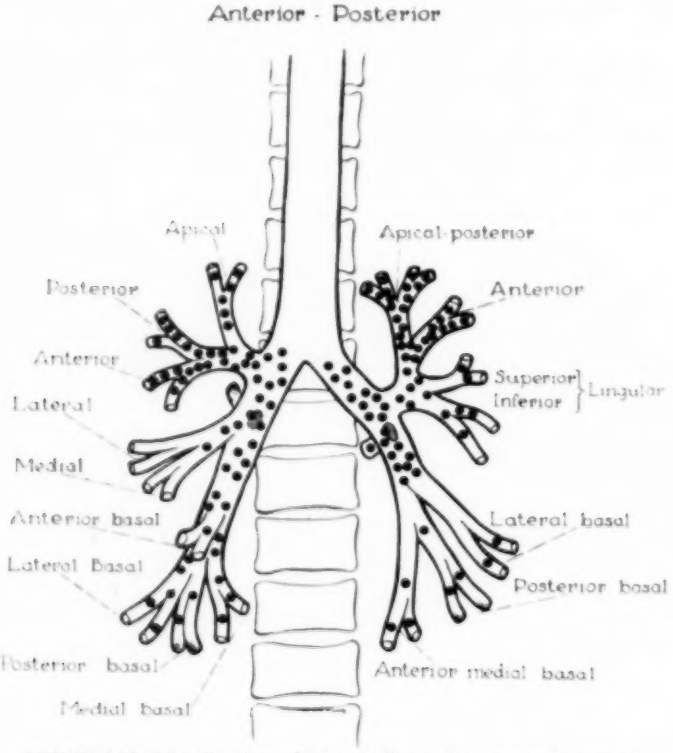

FIGURE 11: Distribution of large cell carcinomas in 130 cases.

the tumors according to the involved lobe in this group of 130 cases. The tumors were approximately evenly divided between the right and left lungs. As one might anticipate, when such a large percentage of tumors occur in the peripheral portion of the lung as they did in this group of 130 cases, bronchoscopy would be less likely to disclose a lesion than it would in cases in which a large majority of the tumors were situated in the central portion of the lung. Bronchoscopy was performed in all of the 130 cases in which resection was performed, and it disclosed a tumor in 65 or 50 per cent of the cases. Biopsy disclosed carcinoma cells in 59 or 45.4 per cent of the 130 cases.

Cytologic examination of the sputum or bronchial secretions was performed in 170 of the 378 cases of large cell carcinoma. This diagnostic procedure disclosed the presence of carcinoma cells in 122 or 71.8 per cent of the 170 cases.

Exploratory thoracotomy was performed in 186 or 49.2 per cent of the 378 cases. Pulmonary resection was possible in 108 or 58.1 per cent of the 186 cases in which an exploratory operation was performed. In 43.6 per cent of the cases in which resection was performed, the patients were alive two years after the operation.

SUMMARY

This report is based on a study of 1,000 cases of proved bronchogenic carcinoma which were observed at the Mayo Clinic. The cell type of the tumors was as follows: small cell carcinoma in 90 cases (9 per cent), adenocarcinoma in 137 cases (13.7 per cent), large cell carcinoma in 378 cases (37.8 per cent), and squamous cell carcinoma in 395 cases (39.5 per cent).

Small cell carcinomas and squamous cell carcinomas occur much more frequently in men than in women. The ratio of males to females was 29:1 in the 90 cases of small cell carcinoma and 25.3:1 in the 395 cases of squamous cell carcinoma. The difference in the sexual incidence was not so great in the cases of adenocarcinoma or large cell carcinoma. The ratio of males to females was 3.4:1 in the 137 cases of adenocarcinoma and slightly less than 6:1 in the 378 cases of large cell carcinoma. The average age of the patients was slightly lower in the cases of small cell carcinoma than it was in cases of the other types of tumor.

The duration of symptoms was shorter in the cases of small cell carcinoma than it was in cases of the other types of tumor. In all of the cases of small cell carcinoma, the patients had symptoms that were referable to the thorax. Such symptoms were not present in all of the cases of the other types of carcinoma. With the exceptions noted, the symptoms were essentially the same in all cases.

Roentgenographic examination of the thorax disclosed an abnormality in all but 12 of the entire series of 1,000 cases. Bronchoscopy was not performed in all of the cases in the respective groups, but it was a very effective diagnostic procedure in cases in which the tumor arose from the central portion of the lung, that is, in cases of small cell carcinoma and in cases of squamous cell carcinoma. Cytologic examination of the sputum or bron-

chial secretions was more effective in the cases of small cell carcinoma and least effective in the cases of adenocarcinoma.

The results of surgical treatment were more satisfactory in cases of squamous cell carcinoma than they were in cases of the other types of carcinoma. The results of surgical treatment were least satisfactory in the cases of small cell carcinoma.

RESUMEN

Esta comunicación se basa en el estudio de 1,000 casos de carcinoma bronquiogénico comprobado que fueron observados en la Clínica Mayo. El tipo celular de los tumores fué como sigue: Carcinoma de celdillas pequeñas 90 casos (9 por ciento); adenocarcinoma en 137 casos (13.7 por ciento), carcinoma de celdillas grandes en 378 casos (37.8 por ciento) y carcinoma de celdillas escamosas 395 casos (39.5 por ciento).

Los carcinomas de celdillas pequeñas y escamosas ocurren mucho mas frecuentemente en el hombre que en la mujer. La relación de hombres a mujeres fué de 29:1 en los 90 casos de carcinoma de pequeñas celdillas y de 25.1:1 en los 378 casos de carcinoma de celdillas escamosas. La diferencia en la incidencia sexual no fué tan grande en los adenocarcinomas o en los carcinomas de celdillas grandes. La relación de hombres a mujeres fué de 3.4:1 en 137 casos de adenocarcinoma y ligeramente menor que 6:1 en 387 casos de carcinomas de celdillas grandes. La edad media de los enfermos fué ligeramente mas baja en los casos de carcinoma de pequeñas celdillas que en los casos de otros tipos de tumor.

La duración de los síntomas fué mas corta en los casos de carcinoma de pequeñas celdillas que en los casos de otros tipos de tumor. En todos los casos de carcinoma de celdillas pequeñas los enfermos tenían síntomas que podían referirse al torax. Tales síntomas no se encontraron en todos los casos de otros tipos. Con las excepciones señaladas los síntomas fueron esencialmente los mismos en todos los casos.

El examen roentgenográfico del torax denotó anormalidad en todos menos 12 casos de los 1,000. La broncoscopía no fué llevada a cabo en todos los casos de los grupos respectivos pero fué un procedimiento de diagnóstico muy efectivo en los casos en que el tumor emergía de la porción central del pulmón, esto es, en los casos de carcinomas de celdillas pequeñas y en casos de carcinoma de celdillas escamosas. El examen citológico del esputo o de las secreciones bronquiales fué mas efectivo en los carcinomas de pequeñas celdillas y menos efectivo en los adenocarcinomas.

El resultado del tratamiento quirúrgico fué mas satisfactorio en casos de carcinoma de celdillas escamosas que en los otros tipos de carcinoma. Los resultados del tratamiento quirúrgico fueron menos satisfactorios en los casos de carcinoma de celdillas pequeñas.

RESUME

Le rapport est basé sur une étude de 1,000 cas de cancers bronchiques observés à la Mayo Clinique. Les différentes formes histologiques des tumeurs furent les suivantes: dans 90 cas, cancer à petites cellules (9%),

dans 137 cas, adénocarcinomes (13.7%), dans 378 cas, cancer à grandes cellules (37.8%) et cancers épidermoïdes dans 395 cas (39.5%).

Les cancers à petites cellules et les cancers épidermoïdes survinrent beaucoup plu fréquemment chez les hommes que chez les femmes. La proportion des hommes par rapport aux femmes fut de 29 pour une, dans les 90 cas de cancer à petites cellules et de 25.3 pour un dans les 378 cas de cancers épidermoïdes. Dans les adénocarcinomes ou dans les cancers à grandes cellules, il n'y a pas une différence aussi nette selon les sexes. Dans les 337 cas d'adénocarcinomes, la proportion fut de 3.4 hommes pour une femme; et un peu moins de six hommes pour une femme dans les 378 cas de cancers à larges cellules.

L'âge moyen des malades fut nettement plus bas dans les cas de cancer à petites cellules que dans les autres formes de tumeurs.

La période symptomatologique fut plus courte dans les cas de cancers à petites cellules que dans les autres types de cancers. Dans tous les cas de cancers à petites cellules, les malades ont présenté une symptomatologie thoracique. De tels symptômes étaient loin d'être présentés dans tous les cas, dans les autres types de cancer. Mis à part ces caractères particuliers, les symptômes furent en gros les mêmes dans tous les cas.

L'examen radiologique du thorax révéla une anomalie dans tous les cas de la série des 1,000 observations, sauf dans 12 d'entre eux. La bronchoscopie ne fut pas pratiquée dans tous les cas, mais elle se montra un procédé très efficace de diagnostic lorsque la tumeur s'était constituée dans une zone centrale, c'est-à-dire dans les cas de cancer à petites cellules et les cancers épidermoïdes. L'étude histologique des crachats ou des sécrétions bronchiques fut le plus efficace dans les cas de cancers à petites cellules et le moins efficace dans les cas d'adénocarcinomes.

Les résultats du traitement chirurgical furent plus satisfaisants pour les cancers épidermoïdes que dans les autres types de cancer. C'est dans les cancers à petites cellules que le traitement chirurgical à donné les moins bons résultats.

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Pulmonary "Coin" Lesions*

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Pulmonary "coin" lesions, as defined by Davis and Klepser,[7] are located in the lung substance, and are round, oval or lobulated, with their edges sharply demarcated and contours smooth, without cavitation and usually without calcification. This group does not include masses with adjacent inflammatory reaction associated with atelectasis or those obviously arising from the chest wall or mediastinum.

These lesions are listed in the literature under various designations, such as single circumscribed intrathoracic densities (Abeles and Ehrlich[1]), solitary intrapulmonary tumors (Davis and Klepser,[7] Effler, Blades and Marks[6]), silent lung disease (Overholt[18]), or isolated pulmonary nodules (Sharp and Kinsella[21]).

The term "coin lesion," however, is descriptive and easily translated into any language. It merits the dignity of a clinical syndrome. While these lesions have been known previously, it was not until Graham, in 1933, found that pneumonectomy was a feasible procedure and, in 1936,[11] reported on three cases of resection of calcified pulmonary abscess (these happened to be tuberculomas) that today's type of study became more practical. With the advent of the mass chest x-ray survey, more of these lesions were brought to light. Alexander[3] called attention to them in 1942. Since that time a considerable literature has accumulated. As Alexander[3] pointed out, these approximately similar x-ray shadows may represent diverse types of benign and malignant lesions. He further stated that any diagnosis from clinical study is of interest but of little importance. What is of paramount importance is whether a nodule is benign or malignant and, if malignant, whether it is still completely removable. Preoperative determination can only rarely be made. Therefore, all presumably removable nodules should be operated upon. There is ample confirmation of this point of view in the current literature from those who are skilled in the treatment of diseases of the chest.

There remains, however, a lamentable reluctance on the part of many physicians, including internists and those specializing in roentgenology, to encourage a patient to have his nodule removed for the purpose of achieving a definitive diagnosis. The vast majority of these silent lesions are discovered on routine x-ray examination of the chest and the patient has no symptom of any kind. As a rule, if the patient does have symptoms, they are not attributable to "coin" lesions. If the physician is reluctant about surgery, how much more likely is the patient to be when such an abnormal condition is discovered. When an abnormal shadow appears on the chest roentgenogram, a tendency to watch it by serial x-ray films over a period

*Presented at the Second International Congress of the American College of Chest Physicians, Rio de Janeiro, Brazil, August 30, 1952.

of time may well eventuate. There is a large gamut of tests now available: examination of the cells and bacteriology of the sputum, if any, and, if no sputum, tracheal wash or gastric lavage; bronchoscopy; various intradermal tests, usually for tuberculosis, coccidioidomycosis, histoplasmosis, and echinococcus; serological tests; various x-ray procedures, including stereoscopic and body section radiography; biopsy of retrosternal and deep supraclavicular nodes, etc. When all of these studies have been accomplished, including, whenever it is thought that such a lesion may be metastatic, gastro-intestinal x-ray series, urological studies with pyelograms, gastroscopies, proctoscopies, x-ray study of the bones, etc., one still sees the shadow on an x-ray film without having achieved a positive and confirmed diagnosis.

Abeles and Ehrlich,[1] in a study of 44 patients carefully worked up, showed that few diagnoses were definitely established before exploratory thoracotomy. In 21 patients operated upon, seven had primary pulmonary malignancies. Ten refused surgery, six of them on the advice of their family physicians, five of the 10 subsequently developed definite malignancy.

Davis and Klepser[7] had a similar experience in some 67 cases, in which 37 (55 per cent), were malignant. In 40 cases referred in private practice, 28 (70 per cent), were malignant, the average age being 52.9 years. In the 67 cases, 47 were males and 20 females, the ages varying from 25 to 74 years.

An Editorial[8] in Radiology, January 1950, on *Pulmonary "Coin" Lesions*, poses the question, "Shall these lesions be observed or operated upon for diagnosis and therapeutic considerations?" It points out that there is a low operative mortality and that there is no other way to achieve a positive diagnosis. In the various series of such patients reviewed and reported, 15 to 30 per cent of the lesions were malignant.

Effler, Blades and Marks,[9] in a study of 24 young service personnel, found that even in this young group 15 per cent of the lesions were malignant, with no mortality from the surgery itself.

Grow, Bradford and Mahon,[12] reporting on 200 young service men hospitalized at Fitzsimons United States Army General Hospital, found 25.6 per cent of such pulmonary lesions malignant.

Mahon and Forsee,[14] in a study of 55 lesions thought to be tuberculomas, reported seven tumors; four (7 per cent) were malignant. Thirteen other lesions were described and the authors state that, in spite of employing every possible diagnostic procedure to arrive at a correct diagnosis, each of these lesions was suspected at some time of being a tuberculoma and only on pathologic examination after removal was the correct diagnosis established. They advise wedge resection to establish diagnosis. They had no operative deaths. It is their belief that in such cases the operative risk is no greater than in appendectomy. Their patients ranged from 19 to 54 years, the average age being 32 years.

Bugden[6] aptly compares the operative procedure in "coin" lesions to that in the study of breast lesions in which biopsy is always accepted.

O'Brian, Tuttle and Ferkaney[16] point out that these lesions will usually fall into one of four groups: (1) malignant or benign tumors; (2) tuber-

culomas; (3) chronic indolent abscesses; or (4) metastatic tumors. In reporting 21 patients over two and a half years of age, in almost 50 per cent of the patients operated upon, the lesion was a tumor and 90 per cent of these tumors were malignant. They point out that a malignant tumor will usually grow but that one cannot wait for this growth for diagnosis, as a small malignant tumor of the lung without growing in situ may metastasize extensively. They further point out that the age of the patient in whom the lesion appears is not always helpful in diagnosis. It is sometimes stated that under the age of 40, because most of these lesions are either benign or tuberculomas, operation is not necessary, but two patients in their series with carcinoma were under 35 years of age and two of the eight patients in their series with tuberculomas were over 50.

Overholt and Schmidt,[17] discussing in 1949 the silent phase of cancer of the lung, stated that the problem was magnified by an astounding recent increase in numbers, yet simplified by facilities for early detection. They pointed out that excision was feasible, relatively safe and effective, and emphasized that physicians now have the tools to find, label and successfully treat cancer of the lung. In 1951, Overholt[18] pointed out that different pathological processes in the lungs may produce identical shadows on x-ray films, while conversely the same disease may produce different shadows. In his series it was impossible to establish an absolute diagnosis preoperatively in more than two-thirds of the patients in whom excisional therapy was indicated. He stated that, in 61 per cent of the cancers seen during the past year, diagnosis could not be established until after exploration. In 162 cases explored, 58 lesions were tumors of which 67 per cent were malignant.

At the Eighth Pembine Therapy Conference, held in September 1951, there was considerable discussion on resection of solitary round lesions.[19] There was almost unanimity of opinion that such lesions should be resected. Attention was called to the fact that the presence of calcification in these lesions does not necessarily rule out the possibility of malignancy.

Schafer and Scott,[20] in discussing in 1947 the general problem of solitary pulmonary "metastases," were of the opinion that, if the primary tumor under consideration seemed to be locally resectable and other inoperable metastases were not present, serious consideration should be given to the possibility that the pulmonary lesion might be a separate disease and amenable to resection. They report such a case in which a giant cell tumor of the right ulna was successfully resected and a "coin" lesion of the left lung, that simulated a metastasis, upon resection was found pathologically to be a hamartoma.

Sharp and Kinsella,[21] in discussing the significance of the isolated pulmonary nodule, reported 96 cases over a four year period. Their patients ranged in age from 12 to 85 years. Growth of a nodule is not necessarily a sign of cancer for it was noted in fibroma, hamartoma, adenoma and granuloma, while lack of growth may be observed in carcinoma for many months. In 41 of their 96 cases, surgical exploration was refused and a confirmed diagnosis was not available. In the other 55 patients the diag-

nosis was proved: 15 (27 per cent), of these were malignant; 22 (40 per cent), inflammatory; and 18 (33 per cent), were benign tumors. The authors concluded that the only reliable and accurate diagnostic procedure is exploratory thoracotomy, with excision and prompt pathological examination of the mass. Even with the lung exposed in the surgeon's hand, it is often impossible to state accurately the nature of the nodule, and they feel that, in general, indirect studies cannot be expected to furnish the answer. At the beginning of their study Sharp and Kinsella made exhaustive clinical studies in attempting to reach a correct clinical diagnosis but concluded that these studies were not worth while.

The significance of calcium in these pulmonary lesions as demonstrated by various techniques, including body section radiography, has been much discussed. Abeles and Chaves[2] report 13 such cases, in five of which the nodule was excised and none was malignant. Eight patients were observed for from two to 12 years and no change was noted, nor was there any evidence of malignancy. They, therefore, consider the presence of calcium strong evidence against malignancy and they feel that such lesions should not be excised, as the exceptions are too few. They advise tomograph films to better delineate the calcific areas. Bloch,[5] in a clinical and experimental study on tuberculous calcifications, concludes that the degree of calcification on x-ray is arbitrary and largely dependent on special x-ray techniques for its demonstration. Davis and Klepser[7] state that calcification suggests inflammatory granuloma, hamartoma, or metastasis from an osteogenic sarcoma. O'Brien, Tuttle and Ferkaney[16] feel that calcium in an x-ray film suggests tuberculosis but is not diagnostic. The 1951 Pembine Conference[19] was in general agreement that the presence of calcification in these "coin" lesions does not necessarily rule out the possibility of malignancy. Sharp and Kinsella,[21] in reporting their 55 proved cases, are firm in stating that calcium deposits do not establish the benign or malignant nature of the process.

Illustrative Cases

Case 1 (Figures 1 and 2): J.N., a 34 year old white male, began, early in 1951, to have vague malaise and easy fatigability and in September 1951, developed a low-grade to moderate intermittent fever, with some cough productive of mucoid sputum, but no blood streaking. Hoarseness and sore throat had also been present intermittently. By the end of October he had lost 10 to 12 pounds and his symptoms had become constant. Chest roentgenogram taken in May 1951, was negative, but that of October 26, 1951, revealed a discrete round lesion in the left lower lung field, measuring approximately 2.5 cm. in diameter on fluoroscopy. Lungs were clear to percussion and auscultation.

Past and Family History: Noncontributory.

Physical Examination: Essentially negative. Blood count and urinalysis were within normal limits. Tuberculin skin tests negative. Agglutinations for typhoid-paratyphoid-undulant fever normal. Bronchoscopy on January 7, 1952, revealed no abnormality.

Exploratory thoracotomy, left, was performed on January 7, 1952, and the lesion was removed.

Pathological Report: The submitted specimen consists of a wedge-shaped segment removed from the lower lobe of the left lung, measuring 4 x 3 x 2 cm. There

is a discrete tumor, 1.9 cm. in diameter, included in this segment. This tumor is of firm consistency, well delineated from the surrounding normal pulmonary parenchyma, and showing on section a firm, gray, laminated surface, having concentric rings similar to those on the cross section of a tree trunk.

Microscopic Description: The microscopic sections taken from the mass described above show it to be composed of rather homogeneous hyalinized connective tissue holding numerous areas of calcification. These masses are seen as purple staining, ghost-like areas, or small concentric laminated, oval-shaped masses. The central area of hyalinization is surrounded by chronic granulation tissue with an occasional multinucleated giant cell. There are scattered round cells, plasma cells, and histiocytes. Acid-fast stains are negative. The histologic picture would be compatible with a chronic granuloma possibly due to *Histoplasma capsulatum*. There is no histologic evidence of malignancy.

Pathological Diagnosis: Chronic granuloma, probably histoplasmosis.

Case 2 (Figures 3 and 4): E.K., a 51 year old white female, had no complaints when first seen in June 1949. An abnormal shadow in the right mid lung field had been discovered in a chest x-ray film survey. A roentgenogram on June 20, 1949, revealed a circumscribed rounded shadow measuring 2.5 cm. in diameter in the

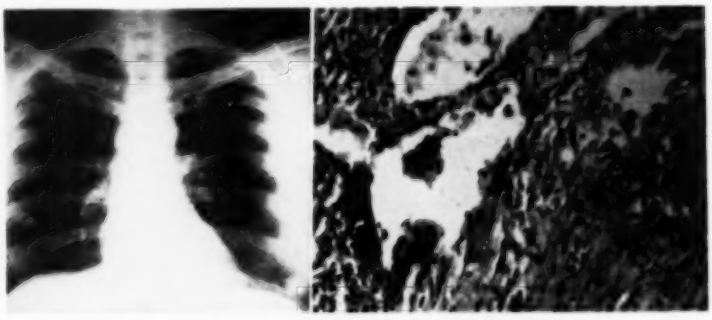

FIGURE 1 FIGURE 2

Figure 1, Case 1: Discrete round lesion in left lower lung field.—*Figure 2, Case1:* Microscopic section. Diagnosis: Chronic granuloma, probably histoplasmosis.

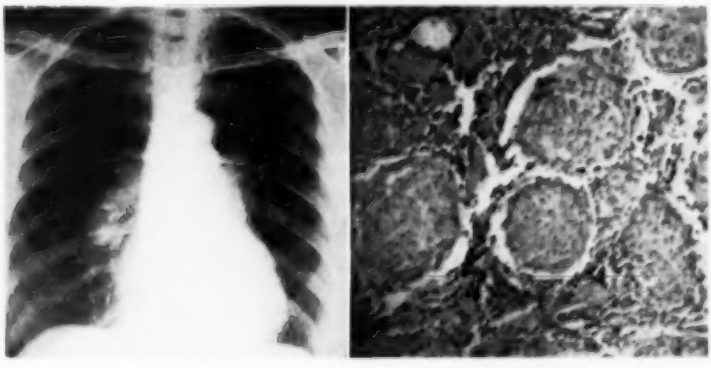

FIGURE 3 FIGURE 4

Figure 3, Case 2: Circumscribed rounded shadow in right lower hilar region.
Figure 4, Case 2: Microscopic section of lymph node. Diagnosis: Boeck's sarcoid.

right lower hilar region. The right basal markings were slightly prominent but there was no parenchymal involvement in either lung. A small amount of calcification was present in the left hilum.

Past and Family History: Noncontributory.

Physical Examination: Essentially negative. Tuberculin and coccidioidin skin tests negative. Blood count and urinalysis were within normal limits. Bronchoscopy on June 28, 1949, revealed normal visible bronchial tree and the Papanicolaou stain for cancer cells was reported negative.

Exploratory thoracotomy, right, was performed on July 25, 1949, and the mass removed.

Pathological Report: The submitted specimen is received in three containers: (1) contains a tumor removed from the right lung, which appears to be a lymph node approximately 4 cm. in diameter, with an irregular red-brown surface. On cut section it has a mottled black appearance interspersed with regions of greyish-white. Sections from here are labeled No. 1. Specimen (2) consists of a small grey-white fragment of tissue removed from the diaphragm, approximately 4 mm. in diameter. Sections from here are labeled No. 2. Specimen (3) contains a mediastinal lymph node, oval in shape, 1 x 0.5 cm. in size. On cut section it is mottled with black but the main portion has a greyish-white structure. Sections from here are labeled No. 3.

Microscopic Description: The microscopic sections of specimen No. 1 show lymph node almost completely replaced by granulomatous tissue arranged in small tubercle-like formations. The lesion is granulomatous and consists of endothelial and fibrous connective tissue cells arranged in a whorl-like pattern. The supporting stroma shows compressed fibrous tissue containing collections of lymphocytes. Also there are regions between these granulomatous lesions where there is a pale pink homogeneous like material. These granulomatous lesions do not show caseation or degeneration. An occasional giant cell is seen. Interspersed in the connective tissue are collections of brown pigment. Sections labeled No. 2 are essentially of a similar pattern and are lymph node almost completely replaced by granulomatous tissue. Specimen No. 3 is a lymph node similar to the other two.

Pathological Diagnosis: Boeck's sarcoid.

Case 3 (Figures 5 and 6): H.B., a 51 year old white male, was well except for frequent colds during 1946 and 1947. Miniature chest x-ray films taken in 1946 revealed an area of infiltration in the lower portion of the left lung field, but nothing was done about it at that time. In November 1947, another roentgenogram was taken and the same finding noted.

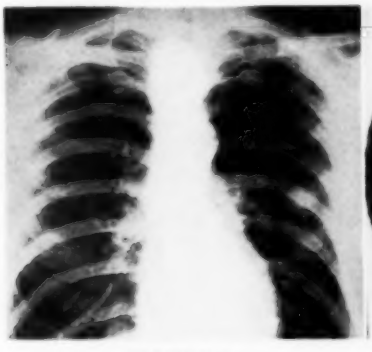

FIGURE 5

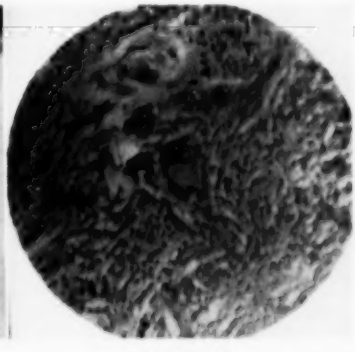

FIGURE 6

Figure 5, Case 3: Mass in left mid-lung field.
Figure 6, Case 3: Microscopic section. Diagnosis: Tuberculoma.

Physical Examination: Essentially negative. Tuberculin test positive. Sputum negative for acid-fast bacilli on concentration. Bronchoscopy was negative.

Exploratory thoracotomy, left, was performed on November 22, 1947, and the lesion removed.

Pathological Report: Submitted specimen consists of the upper lobe of the left lung, measuring 12 x 10 cm. In the central portion, near the hilus, there is a cavity, approximately 3 cm. in diameter, with a thick wall and having a thick inner lining composed of granular necrotic tissue. Surrounding lung is atelectatic.

Microscopic Description: Microscopic sections, taken from the lesion described grossly, show a dense rim of fibrous tissue with the inner lining composed of granulation tissue. This granulation tissue contains large numbers of tubercles with many multinucleated giant cells, clumps of epithelioid cells, round cells and fibroblasts. The surrounding lung tissue shows large numbers of "heart failure" cells within the alveoli. Many areas show atelectasis. There are many areas of caseation.

Pathological Diagnosis: Tuberculoma.

Case 4 (Figures 7 and 8): L.F., a 46 year old colored female, was first seen on August 23, 1948, complaining of tiredness, and pain in the feet, legs and lower abdomen of several months' duration. She had not felt well for five or six years. She had been slowly gaining weight. She had had no cough, pain in the chest, shortness of breath, or hemoptysis. System review was negative.

Past History: Operation for "tumor of the womb" in 1945. Treated eight months in 1945 for "bad blood."

Family History: Noncontributory.

Physical Examination: Negative except for obesity and blood pressure of 154/100. Urine showed albumin, otherwise negative. Blood count normal. Sedimentation rate 23 mm. per hour. Blood Wassermann *positive*. Chest roentgenogram revealed a density in the right lung field about 3 cm. in diameter and calcium in the right hilar area. Sputum was consistently negative for tubercle bacilli on smear and culture. Guinea pig inoculated with sputum was negative for tuberculosis. Bronchoscopy was negative. Secretions aspirated at the time of bronchoscopy were negative for tubercle bacilli and no cancer cells were seen on Papanicolaou stain.

Exploratory thoracotomy was performed on January 17, 1949, and the nodule was removed.

Pathological Report: Specimen consists of a piece of lung with a spherical mass of rubbery tissue 2.5 cm. in diameter. There is no definite capsule visible but the lesion appears to be discrete.

FIGURE 7 FIGURE 8

Figure 7, Case 4: Density in right mid-lung field.
Figure 8, Case 4: Microscopic section. Diagnosis: Bronchial adenoma.

Microscopic Description: Microscopic study shows a tumor mass made up of large numbers of acini lined by tall columnar cells forming what look like bronchioles. The stroma is fine and contains a variety of plasma cells, lymphocytes and mononuclear phagocytes. There is no capsule and the tumor appears to be invading the lung locally.

Pathological Diagnosis: Bronchial adenoma.

Case 5 (Figures 9 and 10): C.B., a 72 year old white male, had a febrile illness of unknown etiology in January 1943. After several weeks of general malaise, anorexia and daily low-grade fever, he developed productive cough and pain in the right axillary line exaggerated by deep breathing and coughing. Chest roentgenogram showed a fairly discrete rounded density lying peripherally in the right lower lung field.

Past History: Dengue fever as a child. Pneumonia many times. Malaria in Mexico when 22 years old. At age of 62 went back to Mexico but had chills and fever so returned to California immediately and symptoms disappeared.

Family History: Noncontributory.

Physical Examination: Negative except for a transient friction rub heard over the right chest anteriorly and moderately enlarged prostate. Blood count normal. Urine normal except for an increased number of white cells at intermittent intervals. Tuberculin skin test was positive. Bronchoscopy was negative. Sputum collected following bronchoscopy was positive for intrathoracic malignancy, Group IV—also many bacteria and pus cells.

There was no definite response to chemotherapy although, over a period of several weeks, the temperature slowly returned to normal. The lesion in the chest remained unchanged.

Exploratory thoracotomy was performed on March 2, 1948, and the lesion removed.

Pathological Report: The specimen is the upper lobe of the right lung. There is a mass felt beneath the pleura laterally toward the lower border, measuring about 3.5 x 3.5 cm. in size. On section the outer portion shows early scar formation; beneath this there is seminecrotic tissue around the central space filled with red-yellow pus.

Microscopic Description: Sections from the solid mass show the outer portion to be made up of fibrous tissue. The alveolar walls are thickened and fibrous. The central area of the mass is completely degenerated and liquefied. There are numerous pus cells present and much cellular debris. At the juncture of the necrotic

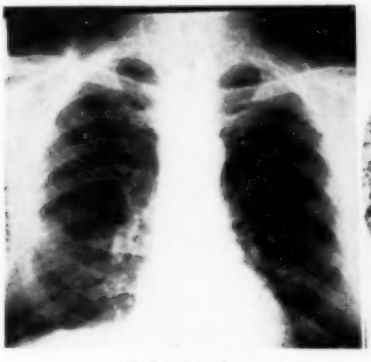

FIGURE 9

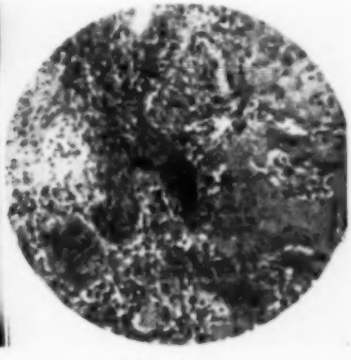

FIGURE 10

Figure 9, Case 5: Discrete rounded density in right mid-lung field toward axilla.
Figure 10, Case 5: Microscopic section. Diagnosis: Squamous cell carcinoma.

tissue in the solid portion of the wall, there are small islands of squamous cells in the solid tissue. These are made up of rather young looking cells with deep staining hyperchromatic nuclei. The squamous cell masses are fairly sharply demarcated but show no basement membrane.

Pathological Diagnosis: Squamous cell carcinoma of the lung.

SUMMARY

In the so-called "coin" lesion, a definitive confirmed diagnosis usually cannot be reached by the various laboratory and x-ray procedures (Aufses[4]). The diagnosis requires surgical exploration, for the removal of the nodule (Effler[10]) and pathological study (Long,[13] Moersch, Weed and McDonald[15]). When this is done, these lesions, many of which look similar on the x-ray film, will finally be diagnosed as a large variety of pathological entities.

The important fact, however, is that in various series from 15 to 30 per cent of the lesions are malignant, and in some specially selected older age groups as high as 70 per cent. Small flecks of calcium, not clearly part of a Ghon complex, do not rule out the possibility that the lesion may be malignant, and they are not a contraindication to exploratory procedures. Exploratory thoracotomy is a benign procedure comparable in risk to appendectomy and should be thought of in the same way as most physicians and even the general public have been educated to think about biopsy of a lump in the breast. The nodule should be removed so that a definite pathological diagnosis can be made. It should not just be watched until a clinical diagnosis can be achieved because by that time metastases are likely to be present and the chance for successful surgery has been greatly reduced. Agreement on these points is almost universal among men skilled in treating diseases of the chest but is not as widespread among the general medical profession and certainly not among the general public. This is a subject, then, that needs continued emphasis.

RESUMEN

En las llamadas lesiones en "moneda" un diagnóstico definido y confirmado no puede hacerse generalmente por los diversos métodos de laboratorio y por los rayos X (Aufses[4]). El diagnóstico requiere exploración quirúrgica para la extracción del nódulo (Effler[10]) y el estudio patológico (Long,[13] Moersch, Weed y McDonald[15]). Cuando éste se hace muchas de estas lesiones que parecen semejantes en la película de rayos X, se diagnóstican al final como una gran variedad de entidades patológicas.

El hecho importante sin embargo es que en varias series, de 15 a 30 por ciento de las lesiones son malignas y en algunos grupos seleccionados especialmente entre las personas de edad el porcentaje llega a 70. Pequeñas precipitaciones calcificadas, que no formen parte bien definida de un complejo de Gohn, no descartan la posibilidad de que las lesiones sean malignas y no son una contraindicación para los procedimientos de exploración. La toracotomia exploradora es un procedimiento benigno comparable en riesgo a la apendicectomia y debe pensarse de ella asi como la mayoria de los médicos y aún el público en general han sido educados para pensar respecto de la biopsia de un nódulo de la mama. El nódulo puede extraerse de ma-

nera que un diagnóstico definido se establezca. No debe solo vigilarse hasta que un diagnóstico clinico se complete porque para entonces es muy posible que ya haya métastasis y las probabilidades de éxito de la cirugia se habrán reducido grandemente. El consenso sobre estos puntos está de acuerdo en esta opinión casi universalmente en la profesión médica y por cierto no lo está en el público en general. Por lo tanto este es un asunto que necesita continuamente ser recalcado.

RESUME

Lorsqu'il s'agit d' "infiltrat rond," le diagnostic en général ne peut être confirmé d'une façon formelle par les procédés variés de labortaoires et de technique radiologique. Pour établir un tel diagnostic, il faut recourir à la thoratomie exploratrice, pour pratiquer l'exérèse du nodule et son étude anatomo-pathologique. Ceci étant réalisé, ces lésions, dont beaucoup se présentent avec le même aspect sur le film radiologique, seront finalement considérées comme appartenant à des entités anatomo-pathologique très diverses.

Toutefois, le fait important est que dans les différentes séries de malades examinés, 15 à 30% des lésions sont malignes et ce pourcentage s'élève jusqu'à 70% dans certains groupes de malades sélectionnés pour leur âge plus élevé. De petites calcifications, quand elles n'appartiennent pas de façon certaine au complexe primaire, ne doivent pas faire exclure la possibilité qu'il s'agisse de lésions cancéreuses, et ne réalisent pas une contre-indication à la chirurgie exploratrice. La thoracotomie exploratrice est un procédé bénin, comparable en risque à l'appendicectomie. On devrait la considérer de la même façon que le font la plupart des médecins et même le grand public quand il s'agit de la biopsie d'une petite tumeur du sein. Il faut extirper le nodule de telle façon qu'un diagnostic anatomo-pathologique puisse être établi. On ne doit pas attendre que le diagnostic clinique soit fait car entre temps les métastases ont tout lieu d'apparaitre, diminuant considérablement les chances d'une heureuse intervention. L'accord sur ces points est généralement universel, parmi les spécialistes de la matière, mais il ne l'est pas autant dans le monde médical en général, et pas du tout parmi le grand public. Il s'agit donc d'un sujet sur lequel il est nécessaire d'insister constamment.

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Hypersensitivity Reactions to Oral Para-Aminosalicylic Acid*

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Introduction

As a result of studies demonstrating its inhibitory effect on the tubercle bacillus in vitro,[1,2] and its therapeutic value in experimental tuberculosis of animals,[3,4] as well as the results of numerous and extensive clinical investigations,[5,6] the role of para-aminosalicylic acid in antimicrobial therapy of tuberculosis has been well established. The tuberculostatic action of para-aminosalicylic acid and its ability to prevent or delay the emergence of streptomycin resistant strains of tubercle bacilli have served to establish the principle of combined treatment with streptomycin and para-aminosalicylic acid as current agents of choice whenever antimicrobial therapy is indicated in the treatment of tuberculosis.

With the customarily employed dosage of 10 to 12 grams daily, para-aminosalicylic acid frequently produces toxic effects which are generally limited to the gastro-intestinal system, in the nature of anorexia, nausea, vomiting and diarrhea. This toxic action, though experienced to a variable degree by a substantial proportion of patients, rarely need cause termination of treatment since the effects can usually be minimized by varying the preparation, meal time administration, and by reduction or temporary discontinuation. On the other hand, subsidence of these toxic effects has also been observed by simply continuing therapy without reduction or modification of preparation or dosage.

In a small but significant proportion of patients at Glenn Dale Sanatorium, unrelated to dosage, there have been observed a variety of symptoms and signs of sufficient acuteness and seriousness to necessarily cause termination of para-aminosalicylic acid. These manifestations which have consisted mainly of chills, fever, rash, headache, transient tender lymphadenopathy, swelling of face and eye-lids, jaundice and eosinophilia, present characteristics of a hypersensitivity type of drug reaction to para-aminosalicylic acid, and have occurred in varying combinations and frequencies in different hypersensitive patients.

In view of the relative paucity of reports[7-15] on this type of reaction, despite the widespread acceptance and use of para-aminosalicylic acid in recent years, adult patients treated with oral PAS at Glenn Dale Sanatorium from September 1951 through April 1952 were closely studied in order to establish the characteristics, incidence and seriousness of hypersensitivity reactions, to observe any correlation with a history or evidence of allergy, and to evaluate the efficacy of a desensitization program.

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Procedures and Methods

This study included all adult patients receiving oral para-aminosalicylic acid, which was dispensed as an aqueous solution of the sodium salt, 12 grams daily, in three divided doses, equivalent to 10 grams of the free acid. Active tuberculosis was present in every patient, so that intermittent streptomycin was given concurrently. Those who developed manifestations known to occur in hypersensitivity reactions to drugs, such as sudden sharp chills and fever, skin rash, facial and eyelid edema, lymphadenopathy, arthralgias and eosinophilia, received special study and investigations designed to establish and confirm a hypersensitivity reaction to para-aminosalicylic acid.

TABLE I
PROGRAMS FOR PAS DESENSITIZATION

Standard			Delayed		
Dosage No.	Daily Dosage	Duration (days)	Dosage No.	Daily Dosage	Duration (days)
1	50 mgm.	2	1	25 mgm.	2
2	100 "	2	2	50 "	2
3	150 "	2	3	75 "	2
4	200 "	2	4	100 "	2
5	300 "	2	5	150 "	2
6	400 "	2	6	200 "	2
7	500 "	2	7	250 "	2
8	750 "	2	8	300 "	2
9	1.0 Gm.	4	9	350 "	2
10	1.5 "	4	10	400 "	2
11	2.0 "	2	11	500 "	2
12	2.5 "	2	12	600 "	2
13	4.0 "	2	13	700 "	2
14	5.0 "	2	14	800 "	2
15	6.0 "	2	15	900 "	2
16	7.0 "	4	16	500 " b.i.d.	2
17	8.0 "	2	17	500 " t.i.d.	2
18	9.0 "	3	18	500 " q.i.d.	2
19	10.0 "	3	19	1.0 Gm. t.i.d.	2
20	12.0 "	†	20	1.0 " q.i.d.	3
			21	2.0 " t.i.d.	3
			22	2.5 " t.i.d.	3
			23	3.0 " t.i.d.	3
			24	3.5 " t.i.d.	3
			25	4.0 " t.i.d.	†

† Continue on full dosage.

In such patients, streptomycin and para-aminosalicylic acid were discontinued, queries were made regarding allergy to drugs, foods, contactants, diseases such as hay fever and asthma, and initial laboratory investigations were undertaken. These consisted of complete blood count including platelet and eosinophile counts, routine urinalysis, Fishberg urine dilution and concentration tests, total protein and albumen/globulin ratio, bromsulfalein liver function test, prothrombin time, icterus index and heterophile agglutination. After an interval of time sufficient to allow for the subsidence of all hypersensitivity signs and symptoms, usually two to four weeks, according to severity, a test or "shock" dose of 0.5 gram of the regular para-aminosalicylic acid solution was given and the patient observed. Recurrence within four to six hours of the identical manifestations which led to cessation of the drug was accepted as final confirmation of a hypersensitivity type of drug reaction to para-aminosalicylic acid. During this recurrence period, the laboratory investigations were repeated, and patch tests were performed with 1 per cent aqueous acetylsalicylic acid, 1 per cent aqueous methyl salicylate, 10 per cent sodium para-aminosalicylic acid and 10 per cent sodium salicylate.

Following the disappearance of all abnormal clinical and laboratory findings, the desensitization program was begun. In general, the method employed was similar to that described by Madigan and co-workers,[12] but differed in that smaller initial dosages were used, and the total program was extended over a longer period of time. Table I lists two programs of desensitization which were successfully used in our patients. The severity of the presenting signs and symptoms determined the selection of the program. The standard program which starts with 50 mgm. para-aminosalicylic acid daily, and covers a period of 46 days, was employed in patients whose hypersensitivity manifestations did not appear severe or potentially

TABLE II

BASIC DIFFERENCES IN CLINICAL MANIFESTATIONS BETWEEN DRUG HYPERSENSITIVITY AND DRUG TOXICITY

Type of Response	*Drug Hypersensitivity* Abnormal, Altered, or Unusual	*Drug Toxicity* Normal or Usual
Relation to Dosage	Occur even to small dosage	related to dosage Proportionately
Predictability	Usually cannot be anticipated in advance	Usually can be anticipated in advance
Manifestations	Essentially allergic	Essentially physiologic or pharmacologic
Specificity	Characteristically nonspecific and variable, with different features in different individuals	Characteristically constant, identical features in different individuals
Mechanism	Immunologic	Pharmacologic
Desensitization	Possible with protein drugs	Not possible or likely

TABLE III: SUMMARY OF HYPERSENSITIVITY DATA IN PATIENTS RECEIVING ORAL PAS

Case Number	1: A.D.	2: I.J.	3: N.P.	4: L.B.	5: G.B.	6: A.V.	7: M.B.	8: M.C.	9: V.M.	10: E.C.	Total
History of Allergy	aspirin	—	—	spinach crab-meat	—	—	aspirin hay fever	penicillin hay fever	—	—	4
Sensitization Period (Days)	9	29	8	31	33	49	37	13	20	28	26
Test Dose	+	+	+	+	+	+	+	+	+	+	10
Drug Fever	+	+	+	+	+	+	+	+	+	+	10
Skin Rash*	m-p	p	pe, e	pa	m-p	m-p	m-p	—	m-p	u	9
Eosinophilia§ (Total)	1082	420	830	820	700	1755	133	500	1340	300	9
Edema of Face and Eyelids	+	+	—	+	+	+	+	—	+	+	8
Yymphadenopathy†	c	c	—	c, a	c	c	c	a, c	—	—	7
Diminished prothrombin time (1 per cent normal)	—	—	45%	45%	45%	—	—	—	—	—	3
Jaundice (Icterus Index)	—	—	—	severe (100)	mild (15)	—	—	—	—	—	2
Thrombopenia	—	—	severe	—	—	—	—	—	—	—	1
Successful Desensitization	+	+	+	+	+	+	+	+	+	+	10

* m - macular; m-p - maculo-papular; pa - papular; pe - petechial; e - ecchymotic; u - urticarial.
§ 250 upper limit of normal.
† c - cervical; a - axillary.

serious. Where such potentially serious manifestations as jaundice or thrombopenia were present, the delayed program which starts with 10 to 25 mgm. para-aminosalicylic acid daily, and covers a period of 53 days, was used.

Discussion

The problem of abnormal or altered reaction capacity to drugs, entirely separate from toxic effects, has long been recognized. When this type of idiosyncrasy is acquired through a mechanism of immunologic hypersensitivity unrelated to known pharmacodynamic characteristics of the drug, the condition is accepted as drug hypersensitivity or drug allergy. The incidence of this phenomenon appears to vary with different drugs as well as with different individuals, and its manifestations may be either generalized or isolated.

The generalized manifestations most commonly encountered, e.g. fever, skin rashes, edema, transient lymphadenopathy and arthralgia, bear a striking resemblance to the syndrome of serum sickness, and have been described following the administration of penicillin, streptomycin, sulfonamides, sedormid, mesantoin, thiouracil and other medications. The important relationship of the hypersensitivity reaction to disease deceived considerable impetus as a result of studies in periarteritis nodosa. The investigations of Rich,[16] and of Rich and Gregory[17] have led to the present opinion that this disease entity is a hypersensitivity reaction which can be caused by widely different antigenic agents such as horse serum, sulfonamides, iodine, desoxycorticosterone acetate and bacteria. Less generalized pictures are seen with such drugs as barbiturates, phenolpthalein, bromides and iodides, known to be responsible for cutaneous rashes with or without fever, and with acetylsalicylic acid, known to cause asthma and rhinitis. The isolated type of drug hypersensitivity or drug reaction may at times be serious. Well known examples of this phenomenon are agranulosytosis caused by aminopyrine, thrombopenia by sulfonamides, arsphenamine or sedormid, jaundice by cincophen, and exfoliative dermatitis by gold compounds.

As pointed out by Black,[18] the distinction between hypersensitive and toxic reactions can usually be made. The basic differential criteria are listed in Table II. In brief, the hypersensitive reaction is an unusual and unexpected one characterized by classic allergic features, such as fever, cutaneous rashes, edema, transient lymphadenopathy, arthralgia and eosinophilia; unrelated to the pharmacodynamic properties of the drug, small doses subsequently given precipitate the same phenomena, which may be variable in different individuals; the underlying mechanism is immunologic and desensitization is possible with protein drugs. On the other hand, the toxic reaction is generally a usual, anticipated one, proportionately related to dosage and pharmacodynamic properties of the drug; it is characterized by constant, identical features in different individuals; the underlying mechanism of the phenomena is pharmacologic and desensitization is not possible or likely.

The unusual features described in Table III, encountered in 10 patients,

were definitely caused by para-aminosalicylic acid, since they were duplicated by small "shock" or test doses after cessation of all medication. On the basis of the differential criteria of the hypersensitivity type of drug reaction discussed above, these patients are considered to have clearly demonstrated hypersensitivity reactions to para-aminosalicylic acid. During the period under observation 255 patients received oral para-aminosalicylic acid, an incidence of approximately 4 per cent.

Though studies of the histologic lesions of drug hypersensitivity have been reported, a review of the literature fails to reveal such report in cases of hypersensitivity reactions to oral para-aminosalicylic acid. An opportunity for histologic study of a lymph node in a patient with a severe hypersensitivity reaction to oral para-aminosalicylic acid became available prior to the time specified in this report, but is recorded here in view of the unusual findings, similar to those reported by Rich. After 26 days of oral para-aminosalicylic acid, this patient suddenly developed fever, pruritis, generalized maculo-papular rash, nausea, vomiting, sore throat, stiffness of the muscles of the neck, generalized tender lymphadenopathy, arthralgia, leucocytosis and eosinophilia. Cessation of all medication was followed by gradual subsidence of these phenomena of hypersensitivity, but a small "shock" dose of oral para-aminosalicylic acid precipitated a recurrence during the same day. During the acute period an enlarged, tender epitrochlear node was biopsied. This was reported by the pathologist as showing "a reactive hyperplasia with marked congestion and some acute adenitis. The hyperplasia is especially pronounced in the reticulo-endothelial elements. A definitely increased number of eosinophiles is present, and some polys are seen. Many of the fine arterioles are thickened. Findings are reminiscent of the sensitivity produced by Rich in animals with sulfa drugs. Impression: reactive hyperplasia of lymph node with adenitis, questionably allergic."

The pertinent data of the patients studied are recorded in Table III. The usual clinical features encountered indicate that sometime during the second to sixth week of daily oral para-aminosalicylic acid administration, generally during the fourth week, the patient experiences an episode of malaise, anorexia, chilly sensations and muscular aches, followed by sudden fever, possibly with a chill. When first seen, the patient appears acutely ill, complains of headache, muscular aches and usually of nausea and vomiting. Physical examination generally reveals the presence of a rash with tender lymphadenopathy and edema of the face and eyelids. Conjunctivitis and pharyngitis are occasionally seen. Laboratory examinations as a rule demonstrate eosinophilia; less frequently diminished prothrombin time, jaundice, and thrombopenia are encountered. The pharyngitis and lymphadenopathy often suggest the possibility of acute infectious mononucleosis, the headache and spasm of neck muscles suggest meningeal irritation.

The following three case reports demonstrate the types of hypersensitivity reactions encountered:

Case 1: A.D. This 36-year old white female, who had never received streptomycin or para-aminosalicylic acid prior to admission, gave a history of allergy to aspirin. Admission leucocyte count was 7,400 with 57 per cent polymorphonuclears, 37 per cent lymphocytes, 5 per cent monocytes, and 1 per cent stab cells. Shortly after admission, on August 27, 1951, she was started on a regimen of streptomycin 1.0 Gm. three times weekly, with oral sodium para-aminosalicylic acid 12 Gms. daily (equivalent to 10.0 Gms. of free acid). On the ninth day of treatment, September 5, 1951, the temperature, which had been normal, suddenly rose to 101 degrees F., followed by a maculo-papular rash, edema of the face and eyelids, and tender cervical lymphadenopathy. During this phase, the leucocyte count was found to be 8,300 with 43 per cent polymorphonuclears, 28 per cent lymphocytes, 3 per cent monos, 1 per cent stab and 25 per cent eosinophiles, and a total eosinophile count of 1,082. On the same day of the reaction, all medication was discontinued, following which all signs and symptoms, with the exception of eosinophilia and lymphadenopathy, disappeared during the next day. After subsidence of signs and symptoms a test dose of sodium para-aminosalicylic acid solution containing 0.5 Gm. was given orally and reproduced all the features of the original reaction in about four hours. One month after the onset of the acute hypersensitivity symptoms, the desensitization program was begun with 0.05 Gm. sodium para-aminosalicylic acid orally. Gradually increasing doses produced no reaction, so that by the 56th day of the program, full oral daily dosages of sodium para-aminosalicylic acid were well tolerated. The patient subsequently had a satisfactory response to combined intermittent antimicrobial therapy and eventually had successful segmental resection.

Case 3: N.P. This 49-year old colored male had not received streptomycin or para-aminosalicylic acid prior to admission on June 15, 1951, and presented no history of allergy. Eight days after the delayed onset of a second course of streptomycin and sodium para-aminosalicylic acid, on November 8, 1951, he developed petechial and purpuric rash with slight fever. A stat platelet count showed no platelets in the peripheral smear. Streptomycin and para-aminosalicylic acid were immediately discontinued, and on the next day the platelet count was 5,000. Over the following days it rose to 166,000 and gradually to normal, as all medications were withheld. Bone marrow aspiration on November 14, 1951, revealed slight erythroblastic hyperplasia, with normal megakaryocytes. Hemogram on November 14, 1951, revealed PCV 39, Hbg 80 per cent, white blood count 9,350 with 61 per cent polymorphonuclears, 18 per cent lymphocytes, 5 per cent monocytes, 2 per cent stabs, 5 per cent basophiles, and 9 per cent eosinophiles, with a total eosinophile count of 830. Blood chemistry and urine studies were normal with the exception of diminished prothrombin time (45 per cent normal). On January 9, 1952, the desensitization program was begun. On the sixth day of the program, with a dosage of 150 mgm., a maculo-papular rash was noted over the back with no petechial or purpuric elements, and without evidence of thrombopenia. After a rest period of 19 days, on February 2, 1952, the desensitization program was begun again, with a smaller initial dose. The program was completed on March 24, 1952, without untoward incident.

Case 4: L.B. was a 28-year old colored female who gave a history of allergy to spinach and crab meat. Otherwise past history was completely negative for recent or relatively remote injections, vaccinations, transfusions or exposure to persons with clinical icterus. Onset of hypersensitivity symptoms was on November 19, 1951, the 31st day after beginning of streptomycin and sodium para-aminosalicylic acid. These were immediately discontinued and the temperature returned rapidly to normal. The test dose on November 29, 1951, reproduced fever, rash, nausea and vomiting. On December 2, 1951, she was noted to be jaundiced and laboratory tests revealed an icterus index of 100, and a thymol turbidity of 57 units. PCV was 44.5, Hbg 13 Gms., WBC 10,150 with 41 per cent polymorphonuclears, 48 per cent

lymphocytes, 3 per cent monocytes, 1 per cent stab cells and 7 per cent eosinophiles. Total eosinophile count was 830. Reversal of the albumen-globulin ratio and a prompt direct Vandenberg were also present. By January 1, 1952, clinical signs and symptoms of hypersensitivity, including jaundice, were no longer present and after another month of careful expectancy the desensitization program was begun with 25 mgm. sodium para-aminosalicylic acid daily (February 8, 1952). This procedure was without incident and full dosage was resumed on March 24, 1952. She is greatly improved and has shown good clinical and radiographic response to combined intermittent antimicrobial therapy.

Present views concerning the mechanism of the development of hypersensitivity to non-protein or crystalloid drugs[18] such as para-aminocalicylic acid are based upon a combination of the drug with protein in the body to form a foreign protein or antigen capable of stimulating antibody production. Landsteiner[19] further postulates that sensitivity to the drug itself occurs after a period of sensitivity to the protein-drug complex. The antibodies however are believed to be fixed to the tissue cells and not circulating or demonstrable in the blood. Consequently, as opposed to allergy to protein drugs which is demonstrable by intracutaneous or patch tests, in allergy to crystalloid drugs these skin tests are uniformly non-contributory and sensitizing antibodies have not been successfully demonstrated.

The diagnosis of drug hypersensitivity to oral para-aminosalicylic acid depends upon the recognition of the clinical manifestations of drug hypersensitivity and the demonstration of para-aminosalicylic acid as the cause. Although the number of cases reported in this presentation is too small to warrant conclusions, it appears that, as in hypersensitivity to other crystalloid drugs, the history of allergic disease and the use of patch tests with para-aminosalicylic acid and chemically related compounds are not helpful in establishing a diagnosis. In general the diagnosis of drug hypersensitivity to oral para-aminosalicylic acid is based upon the occurrence after an initial period of tolerance, of chills, fever, skin rash, facial and eyelid edema, lymphadenopathy, eosinophilia and other untoward manifestations, the rapid disappearance of these manifestations upon cessation of all medication, and their sudden rapid recurrence following a small "shock" or test dose of para-aminosalicylic acid.

Since these hypersensitivity reactions bear no relation either to the history of allergic disease or to diagnostic skin tests, and therefore cannot be predicted or anticipated in advance, no specific prophylactic measures are indicated. However, considerable disability on the part of the patient will be minimized or avoided if the first manifestations of sensitization, usually fever, rash and eosinophilia, are recognized and the use of oral para-aminosalicylic acid is immediately discontinued. The essential aspect of the initial management is the immediate withdrawal of the drug, since this is followed by rapid subsidence of the majority of the clinical features of hypersensitivity within one to five days, depending upon their severity. This abrupt improvement is also of some diagnostic significance. Following withdrawal, only symptomatic and palliative measures, with or without antihistaminics, are necessary. If the causal agent is not withdrawn however, no beneficial response is achieved and the reaction continues. Despite

prompt and striking beneficial response of hypersensitivity reactions to various drugs, reported following the careful use of corticotropin and of cortisone, available current opinions and beliefs regarding these hormones prohibit their use in patients with active tuberculosis.

When hypersensitivity manifestations to oral para-aminosalicylic acid subside upon removal of the causative agent, the problem of its future administration remains. Since best results from antimicrobial therapy of active tuberculosis are often achieved by prolonged combined administration of streptomycin and para-aminosalicylic acid, it is most desirable to overcome the problem of hypersensitivity reactions to the latter by some practical, relatively simple, and harmless procedure which would permit continuation of its use without subsequent reactions.

A cautious program of desensitization to oral para-aminosalicylic acid appears to successfully fulfill these criteria. The two programs outlined in Table I, with minor modifications as dictated by the response and tolerance of the patient, constituted the basic programs of desensitization. Dosage plans were modified, extended or shortened, after the initiation of the desensitization program, as determined by daily observation of the patient's tolerance in terms of hypersensitivity features. Though different patients reacted in a variable fashion to increasing desensitizing doses of oral para-aminosalicylic acid, as long as the initial dose was small, the increase in dosage remained small over a period of time, and the dosage was sharply reduced upon the first manifestation of recurrent hypersensitivity, successful desensitization was possible. This was accomplished in all patients, including two who experienced recurrences during the early phase of the program.

The dosage level of 1.0 to 1.5 grams appeared to be the critical level of tolerance. As this level was approached, reactions recurred in those patients who could not tolerate the increase, thus requiring reinstitution at lower levels with a slower increase rate of dosage. Once the level of 1.0 to 1.5 grams was tolerated without reaction, intolerance to the program was not encountered, and all patients were carried not only to full daily therapeutic dosage of 10 grams orally, but also to subsequent prolonged therapy over several months.

Of interest is the observation that no undesirable effects of the desensitization program were encountered, even in those patients with either initially serious features such as thrombopenia or jaundice or reactions to the desensitization program, since clinical-laboratory studies returned to normal levels in all patients well before reaching full daily therapeutic doses of oral para-aminosalicylic acid. Though one must agree that any desensitization program may theoretically precipitate acute serious reactions, from a practical standpoint results reported here indicate that a cautious, slow program of desensitization in patients who exhibit hypersensitivity reactions, is an effective, simple and safe procedure which can maintain and prolong the therapeutic advantages of para-aminosalicylic acid.

SUMMARY

Hypersensitivity reactions to oral para-aminosalicylic acid have been studied in 255 adults with active tuberculosis, with special reference to incidence, characteristic clinical features, diagnosis and seriousness of the reaction, and value of a densensitization program. Ten cases (4 per cent) demonstrating this reaction are reported.

The hypersensitivity reaction to this drug differs from the toxic reaction in that it is an unusual or unexpected one characterized by classic allergic features, such as fever, skin rashes, facial and eyelid edema, tender acute lymphadenopathy, eosinophilia, and other untoward phenomena; unrelated to the pharmacodynamic properties of para-aminosalicylic acid, small doses subsequently given precipitate the same phenomena, which may be variable in different individuals; the underlying mechanism is immunologic and desensitization is theoretically possible. On the other hand, the toxic reaction is generally a usual, anticipated one, proportionately related to dosage and pharmacodynamic properties of para-aminosalicylic acid; it is characterized by constant identical features in different individuals; the underlying mechanism is pharmacologic, and desensitization is not possible or likely.

The diagnosis of hypersensitivity is based upon the occurrence, after an initial but variable period of tolerance, of chills, fever, skin rash, facial and eyelid edema, tender acute lymphadenopathy, eosinophilia, and other untoward manifestations, the rapid disappearance of these manifestations upon cessation of all medication, and their sudden rapid recurrence following a small "shock" or test dose of oral para-aminosalicylic acid. Despite the acutely ill appearance of the patient and the presence of such serious or potentially serious features as thrombopenia, purpuric eruptions, jaundice and diminished prothrombin time, complete recovery was noted in every case provided the drug was withdrawn.

The problem of hypersensitivity reactions to oral para-aminosalicylic acid was successfully met in each reported case, by a slow and cautious program of desensitization, which was found to be an effective, simple and safe procedure, capable of maintaining and prolonging the therapeutic advantages of this drug in hypersensitive individuals.

RESUMEN

En 255 adultos con tuberculosis activa se estudiaron las reacciones de hipersensibilidad al PAS oral en especial en lo que se refiere a la frecuencia, aspectos clinicos caracteristicos, diagnóstico y seriedad de la reacción y valor del plan de desensibilización. Se refiren 10 casos que demuestran esta reacción (10 por ciento).

La reacción de hipersensibilidad a esta droga difiere de la reacción tóxica es inseperada e inusitada y está caracterizada por los atributos clasicos de la reacción alérgica tales como: fiebre, erupción cutánea, edema de la cara y de los párpados, adenopatía ligeramente dolorosa, eosinofilia y otros fenomenos semejantes, todo esto sin relación con las propiedades farmaco-

dinámicas del PAS; ademas, las dosis pequeñas subsecuentes cuando se dieron precipitaron los mismos fenómenos, que pueden ser variables con los individuos. El mecanismo básico es inmunológico y la desensibilización es teóricamente posible.

Por el contrario, la reacción tóxica es generalmente habitual, prevista, en proporción a la dosis y a las propiedades farmacodinámicas del PAS; está caracterizada por los atributos identicos constantemente en diferentes individuos; el mecanismo básico es farmacológico y la desensibilización no es posible o probable.

El diagnóstico de hipersensibilidad se basa sobre la aparición, después de un periodo variable de tolerancia, de escalofrios, fiebre, erupción cutánea, edema de párpados y de la cara, linfadenopatia con ligero dolor, eosinofilia y otras manifestaciones semejantes, la rápida desaparición de estas manifestaciones al cesar toda medicación y su repentina reapaición después de una dosis de "choque" o de prueba del PAS. A pesar de la apariencia como muy enfermos, y de la aparición de signos tan serios como la trobopenia, erupciones purpúricas, ictericia y disminución del tiempo de protrombina, en los enfermos, en todos los casos se obtuvo una completa recuperación siempre que la droga se suspendió.

El problema de las reacciones de hipersensibilidad al PAS fué atendido con exito en todos los casos referidos por medio de un plan lento y cuidadoso de desensibilización que se encoentró efectivo, sensillo y seguro y capaz de mantener y prolongar las ventajas de esta droga en los sujetos hipersensibles.

RESUME

Chez 255 adultes atteints de tuberculose évolutive, les auteurs ont étudié les réactions d'hypersensibilité à l'administration buccale de P.A.S. Ils se sont particulièrement intéressé à la fréquence, aux aspects cliniques caractéristiques au diagnostic, à la gravité des réactions, et à la valeur qu'on peut attendre d'une désensibilisation. Ils présentent 10 cas (4%) ayant comporté cette hypersensibilité.

La réaction d'hypersensibilité de ce produit diffère de la réaction toxique. Il s'agit en effet d'une réaction inattendue et inhabituelle, qui présente les caractères des signes classiques de l'allergie, avec fièvre, éruptions cutanées, oedème de la face et des paupières, adénopathie aigue, éosinophilie et autres phénomènes d'intolérance. Sans relation avec les propriétés pharmacodynamiques, de petites doses successives entrainent les mêmes phénomènes, qui sont d'ailleurs variables selon les individus. Le mécanisme de tous ces troubles semble être d'ordre immunologique et la désensibilisation est théoriquement possible.

A l'opposé, la réaction toxique est généralement prévisibles, et en relation proportionnelle à la quantité du produit et à ses propriétés pharmacodynamiques. Elle est caractérisée par des symptômes identiques et constants quels que soient les individus. Le mécanisme de tous ces troubles semble être d'ordre pharmacologique, et la désensibilisation n'est pas ou guère possible.

Le diagnostic d'hypersensibilité se base, après une période initiale et variable de tolérance, sur l'apparition de frissons, fièvre, éruptions cutanées, oedème de la face et des paupières, adénopathie, éosinophilie, et autres manifestations d'intolérance, sur la rapide disparition de ces troubles après cessation du médicament, et leur soudaine et rapide réapparition à la suite d'un petit choc ou d'une dose ¿?¿? de P.A.S. par voie buccale.

Malgré l'apparence aigue de la maladie, et la présence de signes qui comportent en eux un pronostic déservé, tels que la thrombopénie, le purpura, l'ictère et la diminution de l'épreuve de la prothrombine, dans tous les cas où l'administration du produit à été cessée, on a constaté une guérison complète.

Le problème de l'hypersensibilité à l'administration buccale de P.A.S. se trouve combattu avec succès dans tous les cas rapportés grâce à une désensibilisation pratiquée lentement et avec précaution. Cette désensibilisation s'est montrée un procédé efficace, simple et sûr, capable de maintenir et de prolonger les avantages thérapeutiques du produit chez les individus hypersensibles.

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Kartagener's Syndrome in Children

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The triad of situs inversus, bronchiectasis and sinusitis has borne the name of Kartagener since this author in 1933[1] collected 11 cases. The first case was reported by Siewert in 1904,[2] in a 21 year old white male, the symptoms having been present since infancy. The literature has been recently well reviewed by Bergstrom, Cook, Scannell, and Berenberg.[3] They collected 80 cases, including two of their own in a family where two additional siblings suffered from bronchiectasis and sinusitis without dextrocardia, and the father from sinusitis only. Zuckerman and Wurtzebach in 1951[4] accepted 40 cases which they collected from the literature as fulfilling the clinical requirements for acceptance to this disease. Their own case was in a 63 year old white male, with symptoms dating back to childhood.

In Bergstrom's and his colleages' series only 16 of the 80 collected cases showed undisputable evidence of bronchiectasis roentgenologically, but in the larger percentage of those in whom history was available, the symptoms dated back to infancy or early childhood, and in 90 per cent symptoms were present before the age of 14 years. Richards[5] reported a case in which symptoms were present on the third day of life.

Many cases described in the recent literature have been of dextrocardia without complete situs inversus, and as these have been generally accepted as valid cases, it would now probably be more fit to describe the syndrome as consisting of dextrocardia, bronchiectasis and sinusitis.

Following are the reports of five new cases.

Case 1: C.M., girl, white, age six weeks. This patient was first seen in Well Baby clinic, with no complaint. The birth weight was 6 pounds, 1 ounce, and she was now 7 pounds, 12 ounces. Physical examination revealed the heart to be on the right side with a loud systolic murmur heard best at the right of the sternum from the fourth to the sixth interspace. Over the chest there were rales with noisy inspiration and expiration. The liver edge could be felt on the left side. There was a slight cyanotic tinge to the skin, but more marked over the extremities. Erythrocyte count was 4,500,000 and hemoglobin 12.2 grams per cent. Roentgenograms showed complete transposition of all the viscera with marked cardiac enlargement. There was a markedly clear periphery of the lung parenchyma (Figure 1). There was little change in the patient's condition, except for frequent colds, until the age of four months, when she was hospitalized with acute pneumonia. From this time on progress was slow. At the age of seven months her weight was 11 pounds. She became increasingly cyanotic and dyspneic. Her erythrocyte count was now 7,600,000, with hemoglobin 11.9 grams per cent; marked microcytosis, poikilocytosis and polychromasia was present. Roentgenograms now showed increased cardiac enlargement, atelectasis of the right lower lobe, and marked pulmonary vascular engorgement of the left lung field (Figure 2). At the age of 10 months she had developed constant nasal discharge, yellow, frothy and mucoid,

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FIGURE 3A

FIGURE 3B

Figure 3A. Case 1: Bronchogram at age of 10 months.
Figure 3B. Case 1: Spot film showing compression of right main-stem bronchus by soft tissue density.

both anteriorly and posteriorly, and roentgenograms revealed very small maxillary sinuses, with no others visible. Bronchoscopy at this time showed the right main bronchus compressed anteriorly and this side could not be entered further. Mucus was aspirated from both sides. Bronchograms showed posterior displacement and partial obstruction to the right main bronchus by soft tissue density, atelectasis of the greater portion of the right lung with irregular small bronchial outlines which could not be evaluated, and probably normal left bronchi (Figure 3). The infant's condition remained the same for some months. She had many upper respiratory infections, cyanosis and dyspnea continued, and she developed marked clubbing of the distal phalanges of all digits. At the age of one year she weighed 13 pounds, 8 ounces. At 14 months she had another acute respiratory infection and died 30 minutes after arrival at the hospital. At necropsy, there was dextrocardia with situs transversus. The heart was markedly distorted, and complete transposition of the great vessels had occurred, i.e., the aorta on the left and pulmonary arteries on the right. Interventricular septal defect was also present. Both lungs were reversed, with two lobes on the right, and four on the left. The right lung was completely collapsed, meaty red and firm, and the left large and fully expanded. The right main bronchus was completely collapsed, and the cartilage in the posterior wall appeared to be absent. Microscopically the right lung showed small focal hemorrhages, the adjoining parenchyma areas of emphysema. There was diffuse disruption of many elastic fibrils. There were larger areas of alveolar hemorrhage in the right lower lobe, infiltrated with numbers of polymorphonuclears and macrophages. The left lower lobe had vast areas of collapsed alveoli with their walls thickened, avascular, and appearing cellular. Many bronchi were collapsed and others contained debris. The right main bronchus presented marked thinning with reduced staining reaction of the cartilage plates. At this point there was angulation and compression of the bronchus wall with narrowing or collapse of the lumen. The mucous membranes were thickened, the glands prominent, and there was diffuse infiltration with lymphocytes and plasma cells. The sinuses were not examined.

Case 2: P.R., girl, white, aged nine years. The complaint was repeated respiratory infections since birth. Atelectasis of the right lung was diagnosed at the age of three days. There was frequent hospitalization during infancy and early childhood for fever, cough and difficult breathing, with cyanosis during the later attacks. At 22 months she had purulent sputum. Pneumonia occurred at least once yearly. There was a constantly running nose between the acute attacks of

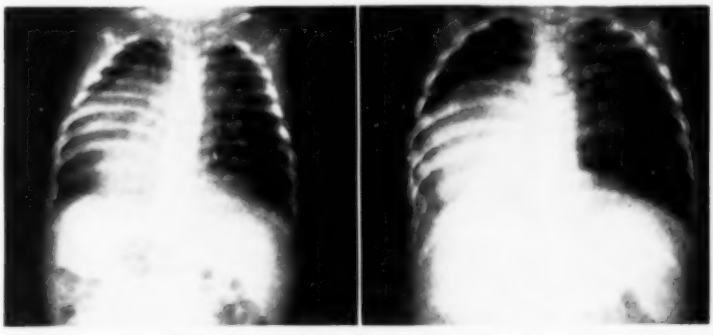

FIGURE 1 FIGURE 2

Figure 1, Case 1: Age six weeks. Complete transposition of viscera, cardiac enlargement, and clear lung parenchyma.
Figure 2, Case 1: Age seven months. Atelectasis of right lower lobe.

cough and fever. Adenotonsillectomy was performed at five years. Physical examination showed a thin, underweight girl, with cough and moderate wheezing. There was mucous discharge from the nose and granular, slightly injected postpharynx with purulent discharge. There were fine and course moist rales, inspiratory and expiratory, throughout the chest. Dextrocardia was present. There was slight clubbing of the fingers. Blood and urine were normal. Trypsin was repeatedly found to be present in the stool. Tuberculin and coccidiodin skin tests were negative. Roentgenograms showed ethmoid and maxillary sinusitis, dextrocardia without complete situs inversus, generalized pulmonary fibrosis, and probable bronchiectasis of the middle and lower left lobes. Bronchograms (Figure 4) showed atelectasis of the left middle lobe with severe saccular bronchiectasis, minimal cylindrical bronchiectasis of the left lower lobe, and possibly saccular bronchiectasis of the right lingula. Resection of the left middle lobe was performed with a wedge resection of the lower segment of the left upper lobe. Gross section of both pieces of lung showed large cylindrical thick-walled fibrotic bronchi filled with purulent material, and surrounded by small amounts of collapsed hyperemic lung tissue. Microscopic examination showed muscular and cartilagenous tissue absent in most of the peribronchial regions and numerous irregular alveolar spaces in the surrounding inflammatory tissue were lined by a conspicuous low cuboidal epithelium. There was dense infiltration of the bronchial walls and surrounding tissue with lymphocytes, plasma cells and eosinophiles in a loose vascular and fibrous stroma. Between the altered bronchi there were varying amounts of pulmonary tissue, some portions of which showed thin-walled distended alveoli, and some alveoli which were compressed, irregular, and contained macrophages, erythrocytes and lymphocytes. Convalescence was uneventful, and she was discharged considerably improved.

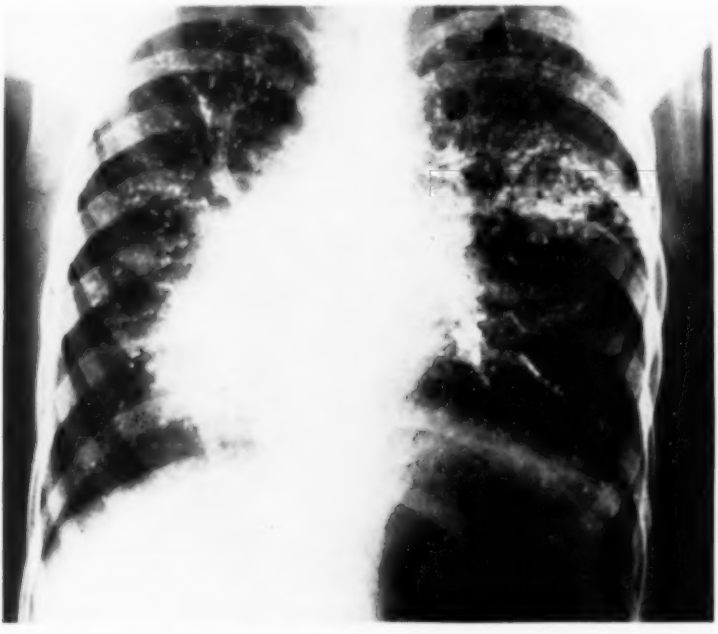

Figure 4, Case 2: Atelectasis of left middle lobe with saccular bronchiectasis.

Case 3: R.T., girl, white, aged 10 years. The complaint was running nose, cough and wheezing since birth. For the past year these symptoms had increased in severity, and she had an afternoon fever. Her brother suffered from a similar condition (Case 4). Physical examination showed a thin, underweight girl. The tympanic membranes were retracted. There was muco-pus on the turbinates and in the post-pharynx. Tonsils were present, and palpable, shotty anterior cervical lymph-nodes. The heart was on the right side. The blood and urine were normal. Tuberculin and coccidioidin skin tests were negative. Roentgenograms showed complete situs inversus and pansinusitis; laminagram showed atelectasis of the left middle lobe (Figure 5). Bronchograms showed marked saccular bronchiectasis of the left middle lobe (Figure 6). Lobectomy was performed, and the gross speciman (Figure 7) showed numerous dilated bronchioles, with thick walls and diameters up to 4.5 mm. throughout the lobe. Histological examination showed most of the lung parenchyma collapsed. There was lymphocytic infiltration diffusely throughout the parenchyma, and in the lumen of the bronchioles some collections of polymorphonuclear leukocytes and lymphocytes in fibrinous material. There was rather marked diminution and destruction of elastic tissue and smooth muscle in the bronchial wall. Some of the bronchial cartilages were partially destroyed. The patient had an uneventful convalescence with marked improvement of her chest symptoms, with absence of fever and diminution of cough. However her sinusitis did not seem to have improved, either symptomatically or roentgenographically.

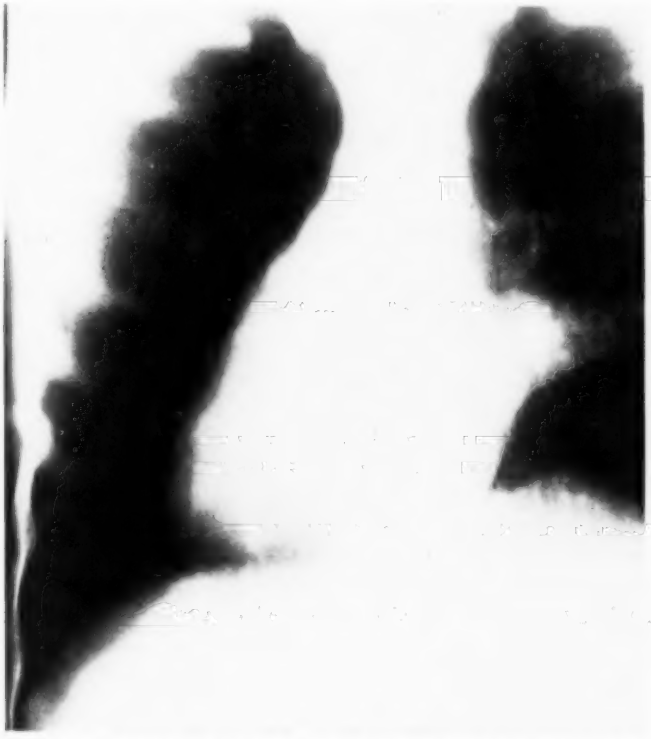

Figure 5, Case 3: Laminagram showing atelectasis of left middle lobe.

Case 4: C.T., boy, white, aged 14 years. The complaint was constantly running nose, chronic cough with sputum, and intermittent fever since early infancy. He had what was diagnosed as an asthmatic attack at five months, and had had them recurrently ever since. He had been treated for chronic sinusitis all his life and had a series of injections for "allergy" without benefit. Adenotonsillectomy was performed at nine years. He had been known to have had nasal polyps for years, with two operations for their removal at ages 10 and 12 years. His cough at entry was productive to the extent of one-half cup of yellowish-white, foul smelling sputum daily. He usually had a low grade fever in the evening. He had been hard of hearing for years. His sister (Case 3) suffered from similar complaints. Physical examination showed a tall thin boy with nasal speech. Both tympanic membranes were fibrotic and somewhat retracted. The right inferior turbinate was markedly hypertrophied, the middle had been removed. The left turbinates were swollen. There was much polypoid tissue on both sides with muco-pus. The posterior pharyngeal wall was covered with hypertrophied lymphoid tissue. In the

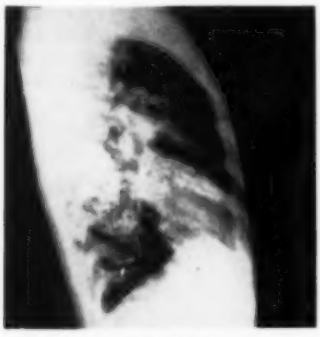

FIGURE 6

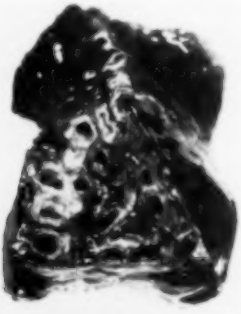

FIGURE 7

Figure 6, Case 3: Bronchogram showing saccular bronchiectasis of left middle lobe.
Figure 7, Case 3: Left middle lobe with dilated bronchioles.

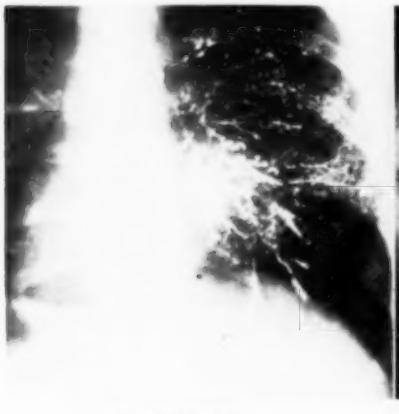

FIGURE 8A

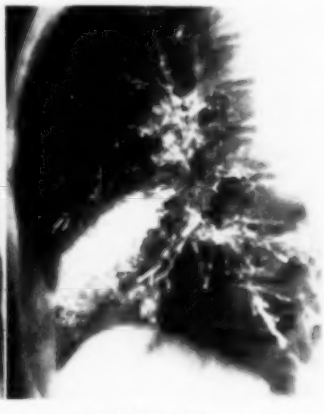

FIGURE 8B

Figure 8A, Case 4: Bronchogram showing tubular and slight saccular bronchiectasis of left middle lobe.
Figure 8B, Case 4: Lateral view.

chest there were coarse wheezes and groans bilaterally with both inspiration and expiration, and fine rales at both bases. Dextrocardia was present. White blood count was 21,100 with 81 per cent polymorphonuclears. Urine was normal. Tuberculin skin test was negative, coccidioidin positive. Roentgenograms showed evidence of pansinusitis, complete situs inversus, and chronc middle lobe disease of the left lung (atelectasis). Bronchograms revealed tubular and slight saccular bronchiectasis of the left middle lobe (Figure 8). Bilateral antral aspiration was done and pus obtained, new ostia were opened and flaps of nasal mucosa laid down. A polyp was removed on the right and a tonsillar tag from the left fossa. Two weeks later left middle lobe resection was performed. Microscopically there was widespread alteration of pulmonary architecture. Varying degrees of alveolar collapse were present with diffuse thickening of the walls of the alveoli by collagenous fibroblastic tissue. Much of the latter was infiltrated with plasma cells and lymphocytes. There were many dilated irregular bronchi and bronchioles, and these showed a replacement of their walls by a vascular fibroblastic tissue diffusely infiltrated with plasma cells, lymphocytes, and scattered eosinophiles. There were areas in the altered bronchioles filled with a polymorphonuclear exudate, and the surrounding parenchyma contained an occasional small abscess. Many irregular alveoli were lined with a dark cuboidal epithelium, and thick-walled arteries and arterioles were numerous. There were scattered areas of hemorrhage into alveoli. After an interval of three months the boy was much improved, his sputum had almost disappeared, but he still had some cough.

Case 5: P.B., girl, white, aged four years. The child came to the out-patient clinic because of pyodermia of the scalp. A history was elicited of chronic nasal discharge since early infancy. A cough was frequently present and this was always worse when she had a cold. She had some improvement after an adenotonsillectomy at two and a half years of age. Dextrocardia was known to have been present at the age of two. She had never had dyspnea, cyanosis, or fatigueability, and had always been very active. Her father had suffered from nasal allergies and sinus trouble. Physical examination showed a well nourished, apparently healthy girl. The nasal passages were filled with mucus which was also present on the postpharyngeal wall. The heart was on the right. A sharp, high pitched, systolic murmur was heard at the aortic area and was transmitted down the right sternal border to the apex. Over the left middle chest there were inspiratory rales. The liver was palpable on the left. The blood and urine were normal. Tuberculin and coccidioidin skin tests were negative. Roentgenograms showed mucosal thickening or exudate in both antra and in the posterior ethmoid air cells, a complete situs inversus, and density in the left middle lobe area suggesting atelectasis or bronchiectasis. Bronchograms visualized all of the principal left bronchial branches and showed bronchiectasis of the left middle lobe with all of the rest of the lung appearing normal. Left middle lobe resection has been advised, but has not yet been performed.

Discussion

In the five cases of dextrocardia, four had complete situs inversus, one dextrocardia only. The case coming to necropsy was found to have other anomalies of the heart. All of the children had pulmonary atelectasis, one on the same side as the heart, the other four on the left side. Four had bronchiectasis in the collapsed lobes on the left, one (the youngest) beginning bronchiectasis or prebronchiectatic changes on the right. All five children had clinical evidence of sinusitis, four had roentgenologic evidence, and in one, the infant, the sinuses were undeveloped. Four of the cases were in girls, one in a boy. The ages at which the disease was diagnosed were 6 weeks, and 4, 9, 10 and 14 years. The 10 and 14 year old

patients were sister and brother. All three children having lobar resections showed considerable improvement of their pulmonary symptoms.

Bronchiectasis seems to accompany dextrocardia or complete visceral transposition in a large percentage of cases. Olsen[6] reviewed the cases of 85 patients with dextrocardia, and found 14 (16.5 per cent) to have bronchiectasis, as contrasted with an incidence of less than 0.5 per cent among all patients at the Mayo Clinic. His study, and that by Adams and Churchill,[7] lend support to the theory that the bronchiectasis in Kartagener's syndrome is congenital in origin. The theory is further supported by many cases in the literature in which the triad occurred in members of the same family, as reported by Bergstrom, et al.,[3] Kaye and Meyer,[5] and ourselves.

European authorities have long favored the congenital theory of origin of bronchiectasis, as opposed to the prevailing opinion in America that most bronchiectasis is acquired.[6] That the congenital theory is not tenable in all cases is proved by the occurrence of the disease following the primary infection with tuberculosis, and following atelectasis from other causes. While in Kartagener's syndrome heredity must usually be the primary factor, or at least predisposing cause, it is conceivable, even probable, that pulmonary collapse may occur after birth in a lobe previously normal, and that bronchiectasis may follow. In the published reports on Kartagener's syndrome bronchiectasis is usually noted as being of the tubular or "varicose" type, instead of the cystic variety generally regarded as congenital.[9] Kaye and Meyer reported a case in which the collapse and bronchiectasis may have been due to the presence of an anomalous left subclavian artery. In the first case of our series there was present a transposition of the great vessels, and the pulmonary changes were those of collapse with only beginning bronchiectasis or a pre-bronchiectatic condition of the walls. In three of our own cases the microscopic changes were degenerative rather than congenital. Bergstrom, et al., from the microscopic findings reported in their case that "the picture was in keeping with the acquired type of bronchiectasis."

Conway[9] believes that the great majority of bronchiectases are acquired, and states: "If it is sometimes congenital it should be possible occasionally to demonstrate it in a stillborn foetus or in a neonate in whom atelectasis or infection have not occurred."

It is our own belief, influenced by a study of the literature and of our own cases, that the sequence of events in the development of Kartagener's syndrome is: 1) congenital anomaly of the cardiovascular system (dextrocardia, sometimes with other anomalies); 2) atelectasis; 3) bronchiectasis, and 4) sinusitis. That the early development of bronchiectasis is influenced by a developmental error in the bronchi themselves is possible, but direct proof is still lacking. There is considerable circumstantial evidence that a congenital factor of some sort is of importance.

The treatment of this disease consists of resection of the affected pulmonary tissue as soon as the patient is deemed a good surgical risk. The

age of the patient in the younger years, after the neonatal period, need not be considered in making the decision. Treatment of sinusitis is indicated, although it is usually not nearly so successful as that of the bronchiectasis.

SUMMARY

1) Five cases of Kartagener's syndrome are reported, all of whom had dextrocardia, atelectasis, early or late bronchiectatic changes, and sinusitis.

2) Lobectomy was performed on three with beneficial results. The youngest patient died before the operation could be performed.

3) From the previously reported cases, and from the present series, it may be concluded that a congenital factor of some sort plays a part in the pulmonary features of the disease. Whether there is a developmental error in the bronchial walls or whether the pulmonary lesions are secondary to the cardiovascular anomalies is still open to debate. In any case, it is probable that in most instances atelectasis precedes bronchiectasis.

RESUMEN

1) Se refieren cinco casos de síndrome de Kartagener, todos los cuales tenían devtrocardia, atelectasia, alteraciones bronquiectásicas tempranas o tardías y sinusitis.

2) En tres de ellos se realizó la lobectomía con resultados benéficos. El más pequeño de los enfermos murió antes de que la operación pudiese ser llevada a cabo.

3) De acuerdo con los casos antes relatados y con la serie presente, puede concluirse que hay un papel que desempeña un factor congénito en las características pulmonares de la enfermedad. Aun esta abierta la discusión acerca de si hay una falla en el desarrollo de las paredes bronquiales o si las lesiones pulmonares son secundarias a las anomalías cardiovasculares. De cualquier modo, es probable que en la mayoría de los casos la atelectasia precede a la bronquiectasia.

RESUME

1) L'auteur rapporte cinq observations de syndrome de Kartagener chez des enfants, dont tous étaient atteints de dextrocardie, d'atélectasie, de modifications bronchectasiques précoces ou tardives, et de sinusite.

2) Une lobectomie fut pratiquée sur trois d'entre eux avec succès. Le plus jeune malade mourut avant que l'opération ait pu être pratiquée.

3) D'après les observations rapportées précédemment et d'après celle-ci, on peut conclure qu'un facteur congénital quelconque joue un rôle dans les symptômes pulmonaires de l'affection. Le débat reste ouvert au sujet de la question de savoir s'il s'agit d'une anomalie de développement des parois bronchiques, ou de lésions pulmonaires secondaires aux altérations cardiovasculaires. En tout cas, il est probable que dans la plupart des observations, l'atélectasie précéda la bronchectasie.

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Adrenal Function in Chronic Pulmonary Tuberculosis*

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The frequency, extent and importance of adrenal involvement in pulmonary tuberculosis, and the role of the adrenal in the clinical symptomatology of this disease have been the subject of widely divergent opinions for many years. This lack of unanimity has a variety of reasons, some of fundamental importance. All too often, judgment as to the presence or absence of adrenal cortical hypo-function has been based solely on clinical criteria such as gastrointestinal disturbances, asthenia, hypotension, and so forth; these symptoms, though usually present in severe adrenal insufficiency, are by no means pathognomonic, and their significance is particularly difficult to interpret in a disease such as tuberculosis where intestinal lesions, malnutrition, and debility are so common. Thorn[1] states, as a matter of fact, that the differential diagnosis of Addison's disease may present great difficulty "in patients with established tuberculosis elsewhere (i.e., *not in the adrenal*) whose excessive weakness, gastrointestinal symptoms or pigmentation raises the question of adrenal involvement" unless detailed studies of adrenal function are performed. The small, globular heart which forms part of the clinical picture of the now discredited "habitus phthisicus" and which was thought to bear some relationship to the small heart commonly found in Addison's disease has been shown by us to have no relation to adrenal function, as far as could be judged by available criteria.[2] Even isolated biochemical data may be misleading in this problem, for low serum sodium values have been observed in patients with chronic pulmonary tuberculosis but without any evidence of adrenal failure.[3] Other biochemical attempts to study adrenal function by highly roundabout means have served only to confuse the picture further. Trautwein,[4] studying liver glycogen in tuberculous patients by indirect tests, found that depletion of liver glycogen exists in such patients, and that repletion could be induced by the administration of adrenal cortical substance. This and similar data were considered to be evidence of adrenal cortical insufficiency. Actually, they merely demonstrate well-known physiological effects of adrenal cortical hormones, and can be observed clinically as well as in starved *nonadrenalectomized* animals. Experiments of this type, then, cannot add to our knowledge of the adrenal status in tuberculosis. Abderhalden and Abderhalden[5] claim that certain urinary proteases reflect adrenal cortical activity. On the basis of this measurement, they state that nearly all severe cases, as well as 36 per cent of "mild" cases of tuberculosis show disturbance of adrenal function.

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The other major difficulty in arriving at unequivocal results has been the manner in which the clinical data were studied. Tuberculous individuals cannot simply be lumped together and treated as a homogeneous group; such a procedure, commonly employed, serves only to produce "statistically insignificant" average values and to mask useful information. Several recent investigations have proved particularly fruitful by their avoidance of this treatment. Pfeffer et al.[6] studied eight individuals with respect to adrenal function and found, in five febrile patients with cavitation and active disease, positive Kepler and Cutler-Power-Wilder tests. The urinary hormone excretion, studied by an unspecified method, was found to be decreased. By contrast, three patients responsive to chemotherapy and improving steadily gave negative tests and normal urinary hormone excretion.

De Figueroa Taboda[7] studied 17-ketosteroid excretion of 79 patients whom he classified carefully according to the degree and activity of their disease, and found that the average values for ketosteroid excretion diminished with increasing severity. Unfortunately, no consideration seems to have been given to sex and age distribution of patients in the various groups; neglect of these factors makes it almost impossible to assess the validity of these ketosteroid measurements.

The most careful report to date is that of Bastenie and Kowalewski,[8] who studied 35 males and 10 females with tuberculosis. All were under 60 years of age. Significant differences were found between the average ketosteroid excretion of normal controls as against the tuberculous patients. However, a breakdown of the clinical material gives a more important insight into their findings: of the 15 with "moderately active" tuberculosis, 14 showed normal urinary ketosteroid excretion, whereas of the 20 classified as "severe," only six were in the normal range and the rest showed decidedly low values. These workers state, "It may be that the tuberculous infection plays the same nonspecific role in depressing adrenal cortical function as other debilitating conditions do."

It is hardly surprising, in view of these diagnostic difficulties, that therapy with adrenal cortical preparations has given inconstant results, and the recent availability of synthetic adrenal steroids such as cortisone has increased the complexity of the problem even further. The data presented by us will attempt to evaluate adrenal function by means of urinary hormone excretion, keeping in mind the possible influence of variables such as age, sex, extent and activity of disease, etc., and may provide indications for adrenal hormone therapy in tuberculosis.

Materials and Methods

Material: A total of 68 patients, 49 males and 19 females, were investigated. In the group under 20 years of age there were three females; in the 21 to 30 year age group there were eight females; in the 31 to 40 year age group there were four females and seven males; in the 41 to 50 year age group there were two females and 11 males; in the 51 to 60 year age group

there were one female and 20 males; in the 61 to 70 year age group there was one female and 11 males. The nature and extent of the tuberculous process was classified according the criteria of the American Tuberculosis Association. One patient was classified in group 2-A, six in group 2-B, one in group 3-A, nine in group 3-B, and 43 in group 3-C.

As a quantitive measure of disease activity the sedimentation rate (Westergren) was used as a convenient index. Seven had a sedimentation rate of less than 10 mm. per hour; nine showed 11 to 25 mm. per hour; 16 showed 26 to 50 mm. per hour; 16 showed 51 to 75 mm. per hour; nine showed 76 to 100 mm. per hour; and 11 a rate greater than 100 mm. per hour.

As major indices of adrenal cortical function, the urinary excretion of 17-ketosteroids and neutral reducing corticoids are used throughout this paper. It should be emphasized, however, that these two parameters do not provide an absolute quantitative nor even qualitative measure of the active function, let alone the reserve strength of the adrenal cortex. Thus any conclusion to be drawn in this investigation regarding adrenal function must be made with this reservation in mind.

Methods: Sedimentation rate was determined by the Westergren method. Total eosinophil counts were determined by chamber count after staining in the pipette with phloxine-methylene blue in propylene glycol. Urinary 17-ketosteroids were determined from pooled 48 hour urines by the method of Drekter et al.[9] Neutral reducing ("11-oxy") corticoids were determined on these same urines by a modification of the method of Heard and Sobel.[10] Blood pressure and weight measurements were performed by the same observer throughout. Determination and evaluation of the cardiothoracic ratio was conducted in the manner described previously.[2] Statistical evaluations were carried out by means of the t-test using the formula

$$\sigma = \left[\frac{\Sigma(x-M)^2}{n-1}\right]^{\frac{1}{2}}$$

FOR THE STANDARD DEVIATION IN GROUPS OF LESS THAN

35 PATIENTS, AND CALCULATING t ACCORDING TO THE FORMULA:

$$t = \frac{M_1 - M_2}{S\left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{\frac{1}{2}}} \quad \text{WHERE} \quad S = \left[\frac{\Sigma(x-M_1)^2 + \Sigma(x-M_2)^2}{n_1 + n_2 - 2}\right]^{\frac{1}{2}}$$

M = MEAN
n = NO. OF CASES
x-M = DIFFERENCE OF ACTUAL VALUE FROM THE MEAN.

Results

Urinary Hormone Excretion. 17-Ketosteroids:

The excretion of urinary 17-ketosteroids is known to vary with age. Moreover, in the male it represents the combined product of testicular and adrenal secretion while in the female the ovary does not contribute to the urinary 17-ketosteroid output. Evaluation of this quantity must, therefore, consider the age and sex factors. Figure 1 shows the individual ketosteroid values of our group of patients distributed according to age and sex. Average values obtained from a considerable number of normals[11] and a range of variation representing approximately one standard deviation is also shown. It is evident that the vast majority of the values obtained fall within the normal range. Sixteen males showed values somewhat higher than one standard deviation above normal; this is not particularly meaningful, for the upward variation in males is quite wide due to the increment of testicular secretion. None of the values fall into the pathologically elevated range. The 10 values in females which appear to be low are actually within the normal range for this sex: to avoid confusion, the normals and normal range for *females* have been omitted from the diagram. Actually, none of the values for women fall in the abnormally low range. Only four male patients in the 55 to 69 year old age group have low values, and of these

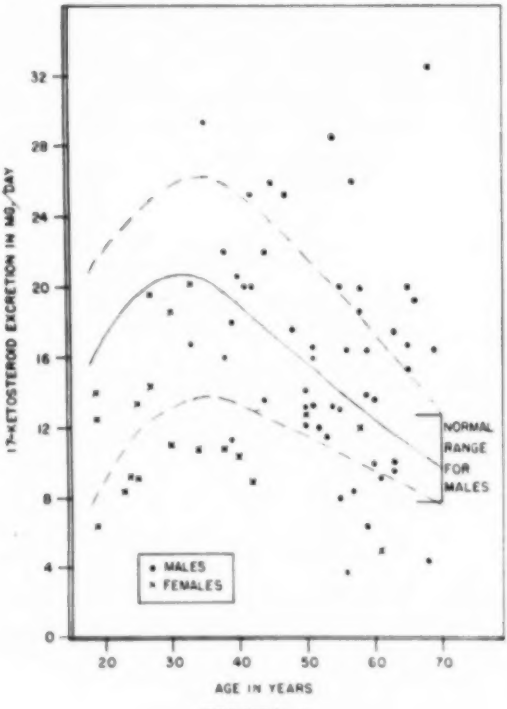

FIGURE 1

only two values are substantially lowered. It may be concluded that urinary 17-ketosteroid excretion (when corrected for sex and age) does not yield evidence of profound adrenal cortical insufficiency in this group of tuberculous patients.

Urinary Hormone Excretion. Neutral Reducing Corticoids (NRC):

As this urinary metabolite is an index of adrenal cortical (and not of testicular) function, males and females show similar levels of excretion. Individual values, plotted against age, are shown in Figure 2. The average value for NRC excretion with age is indicated by a line; the data indicate only approximately the normal range. Once again it is evident that there is no significantly large group of patients whose NRC excretion is abnormally high or low. In this respect the two steroid excretion patterns are in agreement.

Relation of the Sedimentation Rate to Urinary Hormone Excretion:

The sedimentation rate as a convenient quantitative index reflects to a certain extent the activity of the infectious process. To study the rela-

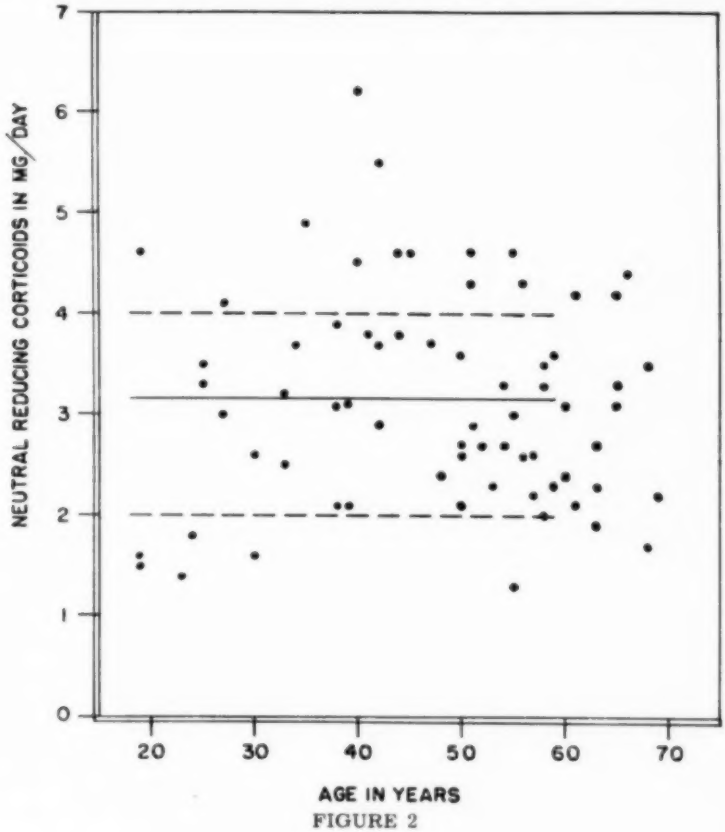

FIGURE 2

tionship of tuberculous activity to urinary hormone excretion, the patients were divided into two groups: those having a sedimentation rate of less than 30 mm. per hour and those with a rate greater than 50 mm. per hour. Each group was adjusted for age and sex distribution. The actual data are summarized in Table I, and their significance is shown in Figure 3.

Statistical analysis of the 17-ketosteroid excretion in these two groups showed a significant difference ($t = 2.1$), which agrees with the findings of other investigators.[6-8] There was also a significant difference in the NRC excretion of the two groups ($t = 2.0$). It may be concluded that adrenal cortical function (as judged by ketosteroid and NRC excretion) is diminished in patients with considerable activity compared to those with minimal or moderate activity as judged by the sedimentation rate.

TABLE I

Sed. Rate in mm./hr.	Number of Patients	Average Excretion in mg. per day	Significance (t-value)
	17 KETOSTEROIDS		
0-30	14	18.6 ± 7.0	2.1
Over 50	32	14.5 ± 5.9	
	NEUTRAL REDUCING CORTICOIDS		
0-30	19	3.5 ± 1.05	2.0
Over 50	33	2.9 ± 0.99	

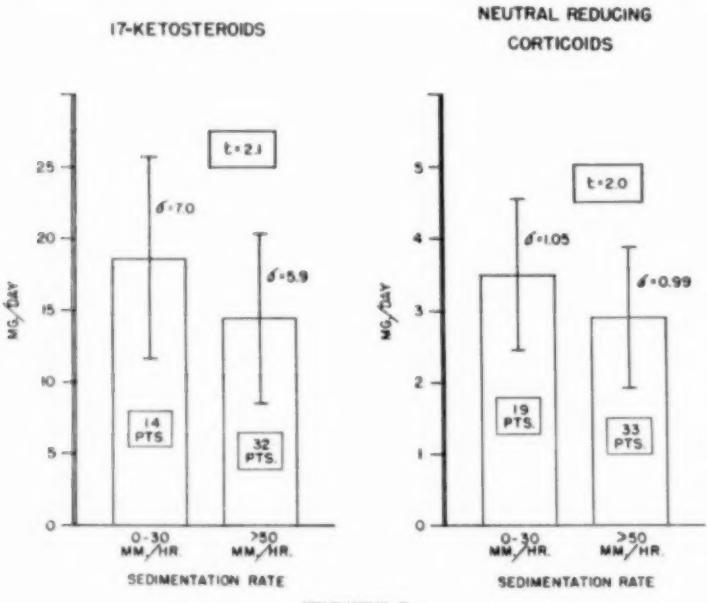

FIGURE 3

Relation of Weight Loss to Urinary Steroid Excretion:

In addition to the sedimentation rate, changes in body weight provide some indication of the activity of the tuberculous process and its effect on the organism. In connection with other studies (to be described elsewhere) the weight was recorded at weekly intervals over a minimum period of six weeks. For purposes of analysis, the patients were divided into two groups: those showing progressive weight loss and those with constant or increasing weight. The data for the urinary hormone excretion of these two groups are shown in Table II.

TABLE II

	Number of Patients	Average Excretion in mg. per day	Significance (t-value)
		17 KETOSTEROIDS	
Weight loss (males only)	6	14.0 ± 2.5	1.3 (n.s.)
No weight loss (males only)	33	17.6 ± 6.8	
		NEUTRAL REDUCING CORTICOIDS	
Weight loss	11	2.6 ± 0.65	1.9
No weight loss	42	3.3 ± 1.2	

The t-value for the comparison between these two groups as regards neutral reducing corticoid excretion is 1.9. Although t±2 is usually selected as the lower limit of statistical significance (equivalent to the 5 per cent level of confidence), one may say that such a correlation is, at least, suggestive. This conclusion would confirm the correlation with sedimentation rate, namely, that increased activity of the disease constitutes an exhausting strain on the adrenal cortex, with a consequent diminution of adrenal activity and decrease in excretory products. And as has been pointed out previously, the lack of confirmation in studies of the 17-ketosteroids is most probably due to the factor of testicular hormone excretion, which is of unknown and variable amount.

Relation of Blood Pressure to Urinary Steroid Excretion:

Hypotension is one of the characteristic findings in adrenal cortical insufficiency and therefore an attempt was made to correlate this clinical sign with evidence of adrenocortical hypofunction as measured by urinary excretion studies. The patients were divided into two groups: the "normotensives" with blood pressure of 100/65 or more and the hypotensives with less than 100/65. Hypertensives were excluded for obvious reasons.

A scattergram of blood pressure vs. hormone excretion failed to reveal any obvious correlation, and therefore a more detailed study by means of the t-test was undertaken. The 17-ketosteroids (corrected for the proportion of males and females) and the NRC values were compared statistically as shown in Table III.

TABLE III

	Number of Patients	Average Excretion in mg. per day	Significance (t-value)
		17 KETOSTEROIDS	
Normotensive	43	17.0 ± 5.7	0.99
Hypotensive	14	12.0 ± 4.2	
		NEUTRAL REDUCING CORTICOIDS	
Normotensive	43	3.2 ± 1.1	1.6
Hypotensive	17	2.7 ± 0.8	

In each instance the difference between the two blood pressure groups was such as could have occurred by chance alone (t 0.99 and 1.6 respectively). It may be concluded that hypotension in the majority of cases, and certainly hypotension alone, cannot be taken to indicate adrenal cortical deficiency in these patients.

The Relation of the Cardiothoracic Ratio to Adrenal Function:

The meaning of the small, spherical heart and the cardiothoracic ratio has been studied previously by one of us as a possible index of adrenal function. By the criteria of that study[2] no correlation could be found. In the present work a further attempt was made to relate the cardiothoracic ratio to adrenal activity, using the urinary hormone excretion as an index of function. A substantial number of patients had to be excluded because of mediastinal deformation due to pulmonary disease; only 40 patients yielded x-ray films in which a determination of the cardiothoracic ratio was meaningful. A scattergram of the cardiothoracic ratios plotted against 17-ketosteroid or NRC excretion failed to reveal any correlation. Because of the nature of the scatter, no further statistical attempt was made to verify the point and we can confirm our previous findings that the small heart in the tuberculous patient is no sign of adrenal cortical hypofunction.

Total Eosinophile Count as a Measure of Adrenal Cortical Function:

It is well known that changes in adrenal cortical activity are reflected in changes of the total eosinophile count. For example, the eosinopenia which follows administration of ACTH has become the basis of a clinical test for the study of adrenal cortical function. The eosinophil counts of these patients were therefore examined in relation to their NRC and 17-ketosteroid excretion. Scattergram analysis failed to reveal any significant correlation. In general, this was to be expected, for it has been observed that *absolute* values of eosinophiles are not useful as an index of adrenal cortical function except in extreme instances. It is usually necessary to study *changes* of total eosinophile count during acute adrenal stimulation. The wide range of the normal total eosinophile count precluded obtaining statistically significant data.

Discussion

Perhaps the most important observation to emerge from these studies is that the adrenal cortex is able to withstand and compensate for the stress of chronic pulmonary tuberculosis in so many cases. This statement, we must emphasize, applies only to the particular type of patient investigated by us, and not to those with an acute, hectic, or rapidly downhill course. The data reveal that patients with a substantially elevated sedimentation rate or progressive weight loss as evidence of active disease do show diminished steroid excretion, indicating adrenal damage and decreased function. In acute febrile conditions generally, the adrenal is known to suffer injury, and this has been shown by others to be true of the acute phases of tuberculosis as well. We agree with Bastenie and Kowalewski that this is not a specific manifestation of tuberculosis in any sense, but a general response to stress whether of infections, toxic, traumatic or other origin.

It seems also that adrenal insufficiency cannot explain the symptoms of asthenia, hypotension or gastrointestinal disturbances in most instances, judging from the efficient adrenal compensation observed in our cases. On the other hand, it must be admitted that minor degrees of adrenal failure, sufficient to produce symptoms but not enough to change steroid excretion (which represents less than 10 per cent of the actual adrenal steroid output) could exist. Investigation of this point must await the development of more refined tests for adrenal activity and reserve.

Lastly, our findings confirm the observation of others, that the adrenal is more or less exhausted in the acute and febrile stages of tuberculosis. As it is solidly established that the adrenal is an important cog in the defense mechanisms of the body, this is a clear indication for the use of adrenal cortical extracts with the potentiating adjuvants thiamine, ascorbic acid and pyridoxine. In this present medical era it is necessary to emphasize that cortical extract therapy is not by any means synonymous with the use of cortisone or desoxycorticosterone acetate (DCA). The former substance particularly, when used in the unphysiological doses currently favored, is known to have just the reverse effect on certain phases of tissue resistance, permitting rather than inhibiting the spread of infection. DCA, in turn, requires constant, careful supervision of electrolyte balance lest edema or potassium depletion be induced, and does not restore normal carbohydrate metabolism or immune response. Cortical extracts by contrast do not produce these side effects even in massive dosage.

In chronic tuberculosis compensated from the adrenocortical standpoint, on the other hand, there seems to be no physiological indication for adrenal substitution therapy.

SUMMARY

The adrenal cortex shows biochemical evidence of damage only during the acute and/or febrile phases of tuberculosis, just as in other stressful situations. In the material studied, which has been carefully defined as to age and sex distribution, type and activity of disease, etc., the degree of

adrenal damage correlated with elevation of the sedimentation rate and progressive weight loss. Clinical symptoms of hypotension (and probably asthenia, gastrointestinal disturbances and so on, as well) cannot be ascribed to adrenal failure without careful biochemical studies. The indications for adrenal cortical therapy are discussed.

Acknowledgments: We wish to express our deepest appreciation to Miss Annabel Schuman and Mr. Edward L. Richman for their management of the nursing and administrative aspects of this project, and to Miss Kate Pollack, Mr. Robert Scism and Mr. Sidney Stern for valuable technical assistance.

RESUMEN

Solo durante las fases agudas y/o febriles de la tuberculosis la corteza suprarrenal muestra evidencias bioquímicas de daño, tal como ocurre en otras situaciones de esfuerzo. En el material estudiado que ha sido cuidadosamente definido en lo referente a edad y sexo, tipo de la enfermedad y actividad de ella, etc., el grado de correlación del daño suprarrenal estuvo de acuerdo con la sedimentación globular y con la pérdida de peso. Sintomas clínicos de hipotensión (así como astenia, trastornos gastrointestinales, etc.) no pueden se atribuidos a falla suprarrenal a menos que se hagan estudios bioquímicos cuidadosos. Las indicaciones para el tratamiento suprarrenal se discuten.

RESUME

Il est démontré par les examens biochimiques que la cortico-surrénale est atteinte exclusivement pendant la période aigue ou fébrile de la tuberculose. Elle se comporte exactement comme dans les autres affections graves. Dans les cas étudiés, qui ont été parfaitement précisés au point de vue de leur âge, de leur sexe, du type et de l'activité de l'affection, le degré de l'atteinte de la corticale est parallèle à l'élévation de la vitesse de sédimentation et à la chute progressive de poids. Les symptômes d'hypotension (et probablement aussi bien l'asthénie, les troubles gastro-intestinaux) ne peuvent être attribués à une insuffsiance cortico-surrénale sans que soient pratiquées des études biochimiques attentives. Les auteurs discutent les indications du traitement par les extraits cortico-surrénaux.

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Cavernous Metastatic Pulmonary Carcinoma
A Report of Two Cases*

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Metastatic carcinoma has been scarcely mentioned as a cause of pulmonary cavitation in the texts and articles on this subject.[1,2] The purpose of this report is to review the literature and to describe the clinical, roentgen and pathological findings in two cases of cavernous metastatic carcinoma of the lungs. In one of these, spontaneous pneumothorax was an associated finding.

Articles pertaining to the roentgen diagnosis of pulmonary metastases stress the classical pictures of nodular, miliary, infiltrative, and massive types. In a 10 year survey of 78 autopsied cases of metastatic pulmonary disease, Farrell[3] reported one with multiple cavities in the lungs due to metastatic sarcoma. Minor[4] reported four with cavernous lesions in a series of 312 cases of metastatic pulmonary carcinoma. The detailed roentgen and pathological findings were not described in these articles. Five cases of spontaneous pneumothorax associated with metastatic sarcoma have been reported; three by Lodmell and Capps,[5] and two by Thornton and Bigelow.[6]

Both of our cases were proved to have rapidly growing carcinomas with widespread metastases. Case 1, a seminoma of the testis, proved at operation, was given x-ray therapy postoperatively. A year later, a chest x-ray film showed solid and cavernous lesions in the lungs. Spontaneous pneumothorax appeared terminally. Metastatic seminoma was found in postmortem aspirations of the pulmonary lesions. Case 2 was found to have solid and cavernous infiltrations in the lungs on admission to the hospital. The lesions in the lungs were suspected to be metastatic on the basis of a Papanicolaou smear of the bronchial secretions. At necropsy, the pancreas was the site of a primary carcinoma and widespread metastases were found in tne lungs and elsewhere.

The metastatic pulmonary lesions appeared similar radiographically in both of our cases and consisted of sharply and poorly circumscribed nodular and irregularly shaped densities and cavities (Figures 1-8). The nodules, in general, were rapidly growing. A nodule in the left lower lobe of Case 1 increased in diameter from 1.0 cm. to 2.5 cm. in about five weeks (Figures 1 and 2). Many of the nodules appeared solid on the initial examinations and apparently excavated into bronchi to form air filled cavities as seen on subsequent examinations (Figures 1-8). This sequence of events is illustrated in Case 1 (Figures 1-4). A nodule behind the heart (Figure 1) excavated to form a cavity (Figure 2) which markedly increased in size

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(Figures 3 and 4). The cavities were generally round, ranging from 1 to 3 cm. in diameter, and the wall thickness from 1 to 4 mm. The lining of the cavities appeared smooth. Several of the rounded thin walled cavities rapidly increased in diameter (Figure 4) resembling tension cavities. A number of nodular metastases, however, increased in diameter similarly, suggesting that the rapid growth of the cavities was due to erosion of the wall by tumor rather than to a bronchial ball-valve mechanism. A cavity in the left upper lobe of one case (Figure 3) showed a fluid level. Spontaneous pneumothorax appeared in the left pleural space with a small amount of fluid. Since an autopsy was not performed on this patient, the mechanism of formation of the pneumothorax could not be determined. The rupture of a subpleural cavity into the pleural space with fistula formation would appear likely.

A host of conditions may cause pulmonary cavitation including tuberculosis, bronchogenic carcinoma, lung abscess, fungus disease, bronchiectasis, cystic disease, infarction, lymphoma and pneumoconiosis. The presence of sharply circumscribed nodular lesions in association with multiple cavities on x-ray of the lungs should suggest the possibility of metastatic disease. Such a diagnosis is supported by the finding of a primary malignant tumor. This form of metastatic disease probably results in extensive erosion of bronchial mucosa so that the Papanicolaou smear of the bronchial secretions should reveal malignant cells in a high percentage of cases. The Papanicolaou smear was highly suspicious of malignant cells in our second case.

We have been unable to determine the exact mechanism of cavity formation in metastatic pulmonary disease from our study of the two cases. Features of these cases suggest several factors which probably play a role. In both instances, the metastatic pulmonary tumors were rapidly proliferating. In all likelihood, the blood supply to such lesions becomes inadequate with central tissue softening and necrosis. Central necrosis was observed in the two cases of metastatic pulmonary sarcoma reported by Thornton and Bigelow.[6] Histologically, in Case 2, the central portions of the lung lesions (Figure 11) consisted of necrotic tissue and numerous segmented neutrophils, indicating the presence of infection. Erosion of the bronchial walls by these lesions and discharge of the centrally necrotic tissue into the bronchial tree would appear most likely although the communications between bronchi and cavities could not be demonstrated at autopsy. Such communications may be extremely difficult to show pathologically. The Papanicolaou smear of the bronchial secretions in Case 2 was highly suspicious of tumor cells. It would seem unlikely that the radiotherapy administered to Case 2 was a factor in the excavation of the pulmonary metastases because the dose administered was small and many of the cavities were outside the treated fields. Many of the solid nodules increased in size at the same rate as the cavities suggesting that the growth of the cavities was caused by erosion of the walls by tumor. On the other hand, the cavities generally appeared almost perfectly round and cystlike indicating the probable presence of a bronchial ball-valve mechanism.

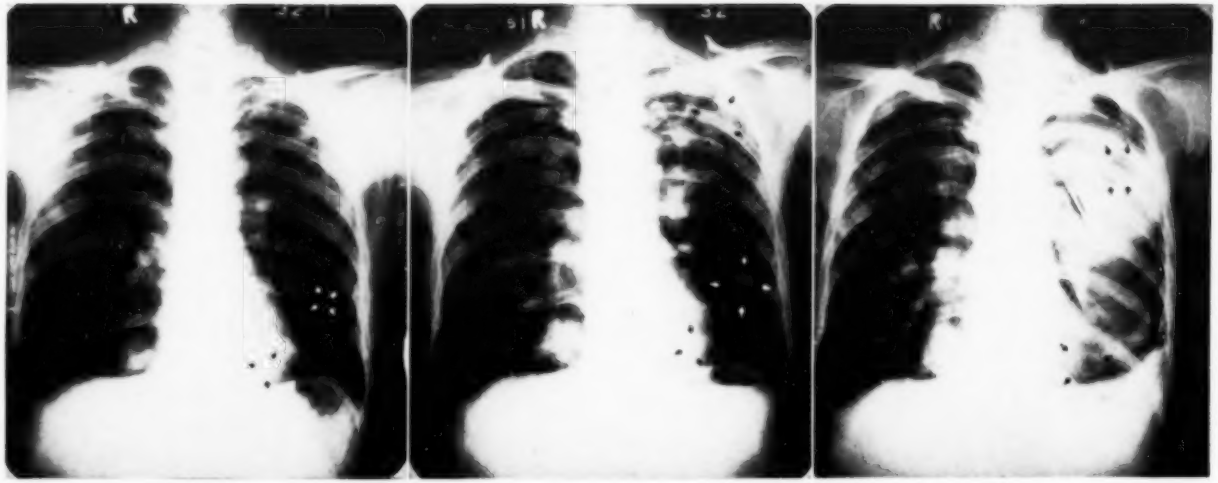

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1, Case 1: Metastatic seminoma. Multiple nodular and irregular lesions scattered through both lungs. Note solid nodule behind heart and at the 5th rib anteriorly.—*Figure 2, Case 1:* Five weeks later, solid lesion behind heart was broken down to form relatively thick walled cavity. Marked increase in size of nodule at 5th rib anteriorly. Cavity at 2nd rib ananteriorly.—*Figure 3, Case 1:* Cavity behind heart has become enlarged and thin walled simulating tension cavity. Left hydropneumothorax. Fluid level in left upper lobe cavity.

Case Reports

Case 1: A 47 year old butcher (L.M., Hospital No. 272752) was admitted to Denver General Hospital January 19, 1951 complaining of low back pain and loss of 80 pounds of weight during the previous eight months. In February 1950 a left orchidectomy was performed at a private hospital in Denver for a tumor which had been known to the patient for two months. X-ray films of the chest, pelvis and an intravenous pyelogram were normal. The pathologic diagnosis was seminoma of the testis. From March 3 to April 13, 1950 he was given postoperative deep x-ray therapy (250 K.V.) directed to the pelvic, aortic, mediastinal, and left supraclavicular lymph nodes, 1200r (air) to each field. Since April 1951 he complained of progressive weight loss and increasing left lower back pain. Physical examination failed to reveal any significant abnormal findings aside from slight tenderness of the lower lumbar spine. Laboratory findings: hemoglobin 12.0 gm.; leucocytes 8,100; neutrophils 85 per cent; lymphocytes 10 per cent; monocytes 4 per cent; eosinophiles 1 per cent. Urine: normal. Two sputum specimens were negative for acid fast bacilli. The Friedman test was negative. X-ray films of the chest showed multiple nodular infiltrations in both lungs consistent with metastatic disease (Figure 1). The intravenous pyelogram was normal. X-ray films of lumbar spine were normal. Radiotherapy was directed to the anterior and posterior abdomen (250 K.V.) 1200r (air) to each field, because of the likelihood that the lumbar spine pain was caused by metastatic retroperitoneal lymph nodes. X-ray film of the chest on February 28, 1951 showed increase in the size and number of the nodules in both lungs, several of which had broken down to form thin walled cavities (Figure 2). On March 22, 1951 a chest x-ray film showed increase in size of several cavities. One in the left upper lobe contained a fluid level. Left hydropneumothorax was present (Figure 3). His condition gradually deteriorated and he expired April 1, 1951. Post-mortem aspirations of the lesions in both lungs revealed necrotic malignant tumor. Comparison of the aspirated tumor from the lung with the primary seminoma to the left testis revealed an almost identical histological appearance.

Case 2: A 65 year old male Negro, pensioner (R.M., Hospital No. 275282) was admitted to Denver General Hospital on May 1, 1951 complaining of epigastric pain

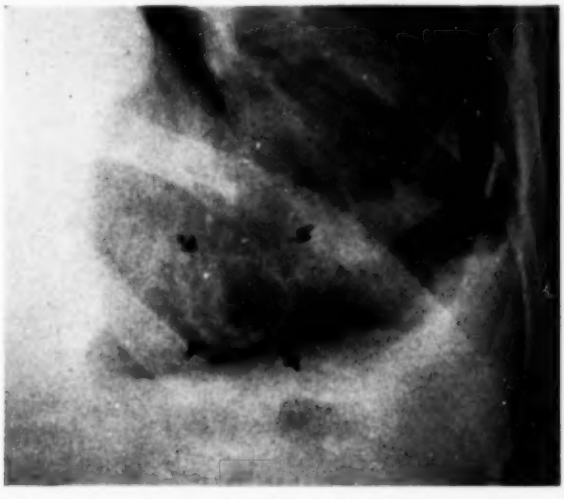

FIGURE 4. Case 1: Close-up of cavity behind heart as seen in Figure 3.

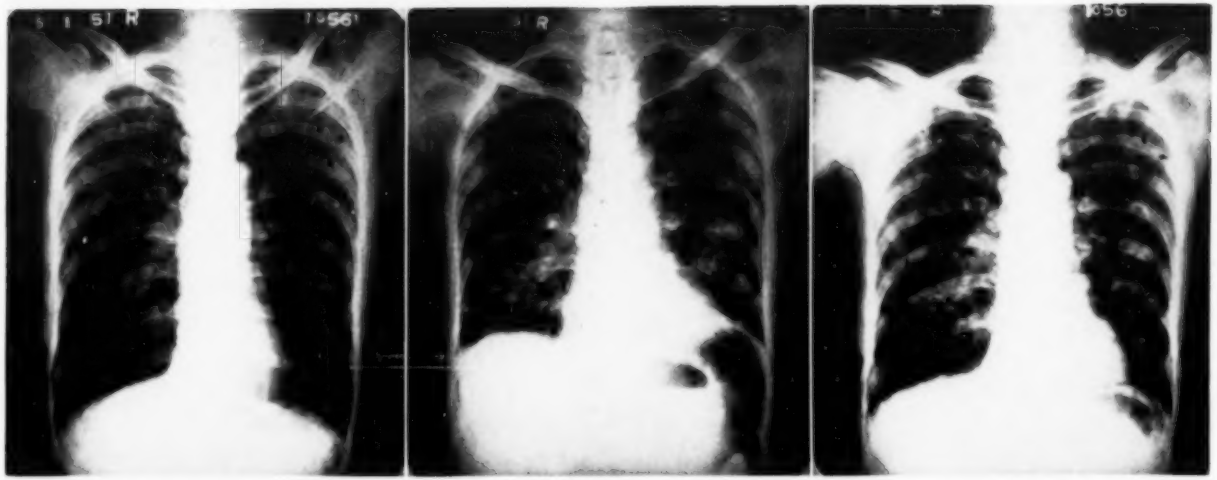

FIGURE 5 FIGURE 6 FIGURE 7

Figure 5, Case 2: Metastatic adenocarcinoma of pancreas. Multiple irregular, nodular, and cavernous lesions in both lungs. A thin walled cavity in left upper lobe is outlined.—*Figure 6, Case 2:* Increase in extent of infiltrations in both lungs.—*Figure 7, Case 2:* Continued increase in extent of infiltrations in both lungs. Note enlargement of thin walled cavity in left upper lobe.

increasing in severity for 10 months. The pain was aggravated by food and occasionally associated with vomiting. During the week prior to admission, he noted three tarry stools. Physical examination revealed that he was chronically ill. There was no other significant abnormality. The urine was normal. Hemoglobin was 13.5 gm.; leucocytes 13,000; neutrophils 69 per cent; lymphocytes 23 per cent; monocytes 9 per cent. Two sputum specimens were negative for acid fast bacilli. Coccidioidin, histoplasmin and tuberculin skin tests were negative. Gastric analysis revealed no free hydrochloric acid. Bronchoscopy was negative. Papanicolaou smear of bronchial secretions was highly suggestive of malignant cells. X-ray film of the chest revealed numerous nodules scattered throughout both lungs, especially in their mid-portions. In addition, there were numerous round cavities scattered through both lungs up to 1.5 cm. in greatest dimension (Figure 5). A gastrointestinal series revealed a small penetrating ulcer on the vertical portion of the lesser curvature of the stomach which had the appearance of a benign peptic ulcer. The antrum of the stomach was inconstantly narrowed. The appearance was consistent with antral spasm associated with the gastric ulcer rather than tumor. A chest x-ray film on May 15, 1951 showed increase in the size and number of the nodules in both lungs. In the lower halves of both lungs, the nodules were confluent. There was a slight increase in the number and size of the cavities (Figure 6). A chest x-ray film on June 1, 1951 showed further increase in the number and size of the cavities (Figure 7). His condition gradually deteriorated and he died on July 3, 1951.

Autopsy: The right lung weighed 1310 gm. and the left 1010 gm. The pleural surface revealed multiple umbilicated lesions with gray borders varying between 0.5 and 1.5 cm. in diameter. On section, the lungs were studded throughout with cavitating lesions measuring up to 5.0 cm. in diameter. The smaller lesions were filled with a soft, dirty gray material, and some of the larger lesions were empty. The walls of the lesions were light gray, well defined, soft and varied in thickness, being 3 mm. thick in the larger lesions. The head of the pancreas was the site of

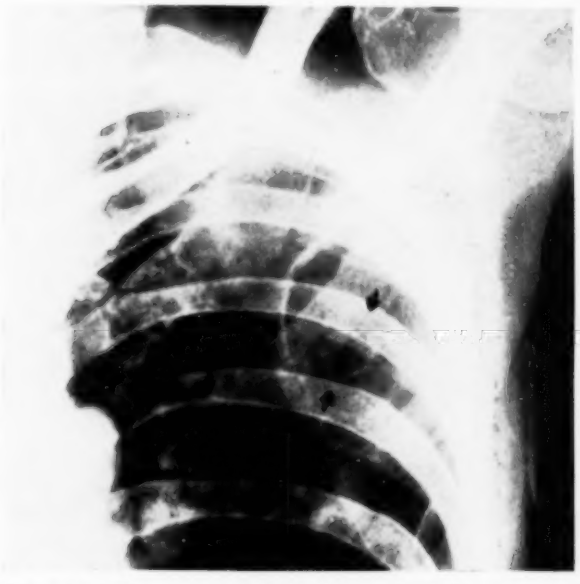

FIGURE 8, Case 2: Close-up of cavity in left upper lobe as seen in Figure 7.

the primary tumor which obstructed the common bile duct causing distention of the gall-bladder, and partially obstructed the pylorus. The tumor was firm, yellow, rounded, imparted a gritty sensation on section, and measured 5.5 x 4.0 cm. A 0.5 cm. gray plaque was present on the mucosal surface of the lesser curvature of the stomach. The liver weighed 1280 gm. and revealed gray-white soft lesions on the cut surface throughout, measuring up to 4.0 cm. in diameter. The serous membranes had an icteric tinge.

On microscopic inspection the pancreatic tumor was a ductal adenocarcinoma with abundant productive fibrosis (Figures 9 and 10). The ducts were atypical and lined by columnar and cuboidal cells having acidophilic cytoplasm, was with

FIGURE 9

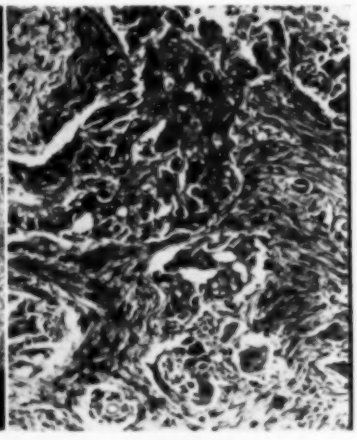

FIGURE 10

Figure 9: Low power of primary pancreatic tumor (x 35).
Figure 10: High power of primary pancreatic tumor (x 125).

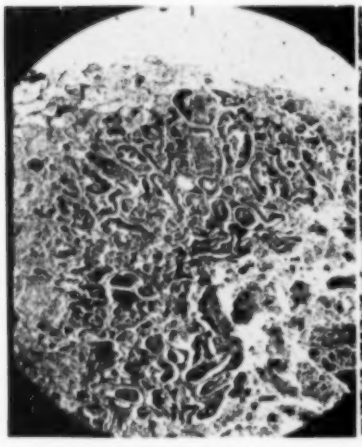

FIGURE 11

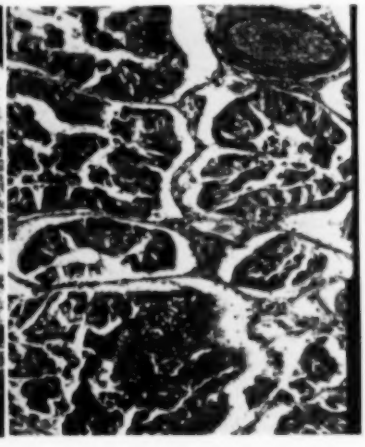

FIGURE 12

Figure 11: Low power of cavitating lung lesion necrotic center at upper right (x 35).
Figure 12: High power of lung lesion (x 125).

hyperchromatic, pheomorphic, and vesicular nuclei. Invasion of blood vessels and perineural lymphatics was noted. The lung lesions revealed the walls to be composed of similar anaplastic ductal structures filling alveoli with central areas of necrosis (Figures 11 and 12). Immediately adjacent to these lesions, the alveoli were stuffed with erythrocytes and groups of tumor cells. Elsewhere the lungs revealed edema, bronchopneumonia, intravascular tumor cells, thrombi, hemorrhagic infarcts and alveoli filled with tumor. Other organs revealing metastatic tumor were heart, liver and adrenals. The stomach lesion consisted of a healing peptic ulcer.

SUMMARY

1) Two cases of cavernous metastatic pulmonary carcinoma have been described. Spontaneous pneumothorax was an associated finding in one.

2) A review of the literature indicates that only four similar cases of cavernous pulmonary metastatic carcinoma have been reported.

3) Rapid growth of the metastatic pulmonary lesions with central necrosis infection and bronchial erosion would seem to be important factors in the pathogenesis of cavernous pulmonary metastases.

RESUMEN

1) Se describen dos casos de carcinoma metatásico pulmonar cavernoso. Un hallazgo asociado en uno de ellos fué el neumotorax espontáneo.

2) Un revision de la literatura ha revelado que sólo se han referido cuatro casos similares.

3) En la patogenia de las metástasis cavernosas pulmonares parece importante el crecimiento rápido de las lesiones pulmonares metastáticas con la necrosis central e infección y la erosión bronquial.

RESUME

1) Les auteurs décrivent deux cas de cancer métastatique du poumon à forme cavitaire; l'un de ces cas s'accompagnait d'un pneumothorax spontané.

2) La revue de la littérature montre que seulement quatre observations similaires ont été jusqu'à présent rapportées.

3) La rapidité du développement des lésions métastatiques avec nécrose centrale infectée et lésions bronchiques paraissent les facteurs importants dans la pathogénie des métastases pulmonaires à forme cavitaire.

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Viability and Chemotherapeutic Sensitivity of Tubercle Bacilli Isolated from Pulmonary and Other Lesions in Embalmed Bodies at Autopsy. Case Report and Clinico-Pathologic Correlation of Cases Studied to Date

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Inasmuch as it is well known that in this country the usual source of tuberculous infection in the human is from another infected human, and much emphasis is placed on careful disposal of infected excreta from living patients, it occurred to us that material from freshly embalmed bodies might retain its infectiousness for a sufficient time after death and embalming to make autopsies on these patients hazardous to the autopsy surgeon, his assistants and observers, especially if they failed to observe proper precautions.[1-3,6] Bodies at this hospital are usually embalmed shortly after death, and autopsy performed on the following day.

This study was done on caseous and fibro-caseous lesions exposed at autopsy. Material from these lesions was cultured for tubercle bacilli to determine whether they were viable after a short period of embalming.[4] The assumption was that penetration of embalming fluid into these lesions was inadequate to kill tubercle bacilli. It is well known that an almost avascular zone of scar tissue surrounds typical old tuberculous lesions, preventing the diffusion of blood-borne agents into them.

Viable tubercle bacilli were obtained in 64.7 per cent of the cases studied to date, as shown in accompanying laboratory data. Upon obtaining the positive cultures, further investigations were conducted as related to para-aminosalicylic acid and streptomycin sensitivity of the organisms isolated in comparison with similar studies on sputum specimens obtained ante mortem. A lack of correlation between results will be noted.

Case Report (Autopsy A-11-51)

This was a 51 year old white male who first developed symptoms of chronic productive cough in 1943 which continued with increasing severity and in April 1948 was accompanied by drenching night sweats and cramping lower abdominal pain. Diagnosis of pulmonary and intestinal tuberculosis was established at that

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

time, and he was referred to this facility. Physical examination was not remarkable aside from marked malnutrition, signs of consolidation with fine, moist rales over the upper half of the right lung, upper third of the left lung, and abdominal tenderness over the course of the ascending colon. Chest film revealed mottled, confluent, fibro-caseous infiltrations of heavy density involving the right lung from the apex to the fourth anterior intercostal space, with an area of rarefaction in the second interspace suggesting cavitation. On the left was a thickened pleural cap with a large area of rarefaction involving the sub-apex and first intercostal space, confluent infiltration of moderate density involving the remainder of the lung. Sputum was positive for acid fast bacilli on direct smear. Sigmoidoscopy was negative and barium enema showed no demonstrable pathology of the colon or terminal ileum. Stool examinations were negative for blood, ova and parasites. The white blood cell count was 12,000, 85 per cent neutrophils, 15 per cent lymphocytes. Sedimentation rate 29 mm. per hour. Urinalysis negative. Kahn, negative. He was placed on a conservative regimen of bed rest and sanitorium care, with gradual symptomatic improvement. However, he showed little objective change. Shortly after admission he developed hoarseness and pain on swallowing, associated with edema and ulceration of the larynx which was treated with streptomycin 1 gram daily and para-aminosalicylic acid 12 grams daily. On this treatment his throat symptoms promptly subsided. Streptomycin was stopped after 56 grams because of vertigo. Para-aminosalicylic acid was continued to a total of 120 days. No measurable improvement of lung lesions was noted following streptomycin treatment. His generalized abdominal soreness associated with cramping, postpranial pain showed moderate improvement during and after streptomycin administration and this drug was given intermittently during the remainder of his hospital stay, chiefly to control abdominal symptoms. He developed profound hypochromic microcytic anemia which necessitated transfusions, and he received a total of seven transfusions of 500 cc. of whole blood throughout the remainder of his hospitalization. Sputum continued positive and showed partial resistance to para-aminosalicylic acid, with two plus growth at 10 mg. per 100 cc. solid egg medium. In vitro sensitivity to streptomycin remained with no growth at 10 micrograms per 100 cc. solid egg medium. He continued to run persistent evening fastigium and became progressively more cachexic and expired April 30, 1951. Clinical diagnoses: (1) Pulmonary tuberculosis, reinfection type, far advanced. (2) Tuberculous enterocolitis, treated, improved. (3) Anemia due to chronic loss of blood.

Postmortem Observations (A-11-51):

Autopsy Summary: Autopsy revealed a 51 year old emaciated, 95 pound male, measuring 155 cms. in length. The right lung weighed 760 grams, and there was a thick, tough, fibrous roughened pleura. In the upper lobe, there was a 4 cm. multiocular cavity containing caseous, greenish-yellow debris. The lining of the cavity was ragged and had a leathery appearance on removal of the exudate and there was found a large communication with one of the major bronchi of the upper lobe of the right lung. The middle lobe of the right lung contained a 3 cm. cavity filled with necrotic debris. The lower lobe and the remaining lung parenchyma contained scattered, brownish foci of induration and dullness. The left lung weighed 750 grams. Its outer surface was also rough and it had a 7 cm. cavity in the upper lobe, also containing caseous exudate and it also had a communication over the larger upper lobe bronchi. The remainder of the upper lobe and the lower lobe contained many scattered opaque yellow caseous foci, which were well circumscribed, lobulated and measured up to 2 cms. in diameter. Microscopic studies showed active caseous and fibrocaseous lesions characteristic of the gross lesions.

Other significant findings were hypertrophy and dilation of the right side of the heart, acute ileitis, fatty metamorphosis of the liver, chronic cholecystitis and cholelithiasis and a remarkable lack of the arteriosclerosis throughout.

Final Diagnosis:

1) Marked fibrocaseous active tuberculosis with large cavities of right upper and middle lobes and left upper lobes with demonstrable bronchial communications.
2) Tuberculous bronchopneumonia.
3) Tuberculous ileitis and ascending colitis.
4) Marked emaciation.
5) Right ventricular hypertrophy and dilatation.
6) Chronic cholecystitis with cholelithiasis.
7) Passive hyperemia of the lungs, liver, spleen and kidneys. Fatty metamorphosis of the liver.

Laboratory Examinations:

Commercial type embalming methods were used under contract with a professional embalmer. Between 20 and 33 ounces of concentrated arterial embalming fluid was injected over a few hours period. No cavity embalming was performed. A trade name arterial embalming fluid was used. Although the actual ingredients of this fluid is unknown to us, most of the fluids have the following ingredients in these proportions: 1) Formalin, 8.5 per cent; 2) Glycerol, 2 oz.; 3) Boric acid, 8 gm.; 4) Iso propol alcohol, 2.5 oz.; 5) Potassium nitrate, 15 gm.; 6) Sodium citrate, 6 gm.; 7) Methol salicylate, 3 cc.; 8) H_2O, 2.5 oz.; 9) Dye, 1 cc.; 10) Formalin index means per cent of formaldhyde in fluid. Most commercial fluids have an index of 20 or approximately 20 per cent.

Table I shows the time elapse between embalming and autopsy of the cases studied and the viability results of cultures for the tubercle bacilli.

It is observed from Table I that 64.7 per cent of the material from autopsy cases studied to date resulted in cultures positive for tubercle bacilli. Caseous cultural materials were collected with sterile swabs after slicing into the cavities. The trisodium phosphate concentration method was used and these concentrates were cultured on Jensen-Lowenstein's solid egg medium. The positive cultures were all heavily positive with growth varying from innumerable colonies on the medium to the surface being entirely covered. In the samples taken where the embalming fluid was grossly present such as the IV ventricle in case (A-4-51) and the brain in case (A-34-51), no viable organisms were isolated. The positive cultures were obtained from the areas of caseous and fibro-caseous cavities where the embalming fluid had apparently not penetrated.

Sensitivity results as related to the region isolated (from autopsy specimens) and the comparison of these sensitivities with sputa samples obtained prior to death are given in Table II with emphasis on Case A-11-51.

Comparable para-aminosalicylic acid sensitivity results were obtained in Case A-11-51 between the right apex sample and a sputum obtained on September 20, 1950. The streptomycin sensitivity results were comparable with the sputum from all samples tested on A-11-51. Variations between the para-aminosalicylic acid sensitivity of September 20, 1950 is noted from the other samples obtained at autopsy. In the case of A-7-51, a disagreement was noted between the sputum and the samples obtained from the cavities studied. Many more autopsy samples of this nature would be necessary to arrive at any definite conclusions although it would seem that the type of lesions as to the amount of fibrosis and the communication

TABLE I: Interval Embalming to Autopsy and Viability Results of Cultures.

Autopsy No.	Approximate Time of Embalming*	Autopsy Performed	Interval Embalming to Autopsy	Viability Results (Tubercle Organisms)
A-34-50	9:30 AM 12-7-50	12:30 PM 12-8-50	27 hrs.	(Meningitis) Right Lung—Negative. Left Lung—Negative. Brain—Negative.
A-36-50	1:30 PM 12-7-50	10:45 AM 12-8-50	20 hrs. 15 min.	Right Lung—Negative. Left Lung—Negative.
A-3-51	10:30 PM 2-23-51	11:45 AM 2-26-51	61 hrs. 15 min.	Lung—Positive.
A-4-51	11:00 AM 3-9-51	10:30 AM 3-10-51	23 hrs. 30 min.	(Meningitis) IV. Ventricle—Negative.
A-7-51	Unknown 3-14-51	11:15 AM 3-15-51		Left Lower Lobe—Positive. Left Upper Lobe—Positive.
A-11-51	5:40 PM 4-30-51	3:30 PM 5-1-51	21 hrs. 50 min.	Left Apex—Positive. Right Apex—Positive. Left Upper—Positive. Right Middle—Positive.
A-15-51	4:00 PM 7-2-51	3:00 PM 7-3-51	23 hrs.	Right Lobe (a)—Positive. Right Lobe (b)—Positive. Apex Left Lung—Positive. Right Upper Lobe—Positive.
A-18-51	12:30 PM 7-28-51	10:00 AM 7-30-51	45 hrs. 30 min.	Right Upper Lobe—Positive.
A-20-51	7:20 PM 8-9-51	10:00 AM 8-10-51	14 hrs. 40 min.	Right Upper Lobe—Positive. Right Lower Lobe—Positive.
A-23-51	11:00 PM 8-26-51	1:30 PM 8-27-51	26 hrs. 30 min.	Abscess axilla)—Negative. Lung—Negative.
A-24-51	11:00 AM 9-1-51	11:00 AM 9-2-51	24 hrs.	Middle Lobe—Negative. Mediastinum—Negative.
A-28-51	7:20 PM 10-9-51	10:00 AM 10-10-51	14 hrs. 40 min.	Base Left Lung—Positive. Right Lower Lung—Positive. Left Lower Apex—Positive. Left Apex—Positive. Trachea—Positive.
A-29-51	3:40 PM 10-11-51	15:45 AM 10-12-51	19 hrs. 5 min.	Prostate—Positive. Right Lower Lung—Negative. Left Lower Lung—Negative. Left Upper Lung—Positive. Right Upper Lung—Negative.
A-30-51	11:30 AM 10-11-51	12:20 PM 10-12-51	24 hrs. 50 min.	Right Middle Lobe—Negative. Left Lung—Negative. Right Lung—Positive.
A-31-51	5:30 PM 10-14-51	11:00 AM 10-15-51	17 hrs. 30 min.	Right Lobe Apex—Positive. Lung Apex—Positive. Right Lung—Negative. Right Lower Lung—Positive. Right Upper Lung—Negative.
A-32-51	12:30 AM 10-14-51	1:30 PM 10-15-51	25 hrs.	Left Upper Lung—Negative. Right Upper Lung—Negative.
A-34-51	10:10 AM 11-14-51	1:00 PM 11-15-51	26 hrs. 50 min.	Left Upper Lung—Negative. Left Lower Lung—Positive. Emphysema (cavity)—Pos. Apex Left Lower Lung—Neg. Left Seminal Vesicle—Pos.

Note: Bodies were refrigerated after embalming until the time of autopsy. (The temperature coefficient of formaldahyde solution is rather high?).

with bronchi would influence variations in sputum sensitivity results. The variations in sputum sensitivities could then be accounted for by their regional source or type of pathological lesion from which the particular material in the sputum originated. This is especially true in the tuberculous lesions.

SUMMARY

1) Caseous and fibrocaseous tuberculosis may contain viable tubercle bacilli in large numbers prior to and after a short embalming period. Pathologists, observers and other personnel handling these materials should adhere to safety measures in order to prevent accidental infections.

2) Chemotherapeutic sensitivity results in tuberculosis may vary in the same individual depending upon the type of lesion and source from which the tubercle organisms are obtained as shown in our data by the sputa and autopsy materials studied.

TABLE II: Comparison of Sensitivity Findings From Autopsy and Sputa Samples Obtained Prior to Death.

Autopsy No.	Sensitivity Results, Sputa Cultures	Sensitivity Results on Positive Autopsy Cultures
A-3-51	None performed prior to death.	Sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.
A-7-51	On 1-19-50 and 2-15-50 sensitive to SM at 10 mcgm S/cc.	*Left Lower Lobe:* SM, partial resistance at 10 mcgm S/cc. Sensitive to PAS at .1 mgm/100 cc. *Left Upper Lobe:* Partial resistance to SM at 10 mcgm S/cc. Sensitive to PAS at .1 mgm/100 cc.
A-11-51	Twenty sputum tests between 3-23-49 and 3-4-51 show SM sensitive at 10 mcgm S/cc.; partial resistance to PAS at 10 mgm/100 cc.	*Left Apex, Left Upper and Right Middle Lobes:* Sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc. *Right Apex:* Sensitive to PAS at 10 mcgm/100 cc.; sensitive to SM at 10 mcgm S/cc.
A-15-51	None performed prior to death.	*Right Lobe (a), Right Lobe (b), Apex Left Lung and Right Upper Lobe:* Sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.
A-18-51	Partial resistance to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.	*Cavity Right Upper Lobe:* Sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.
A-20-51	Four cultures from 9-13-50 to 7-18-51 show sensitive to SM at 10 mcgm S/cc.	*Right Upper Lobe:* Partial resistance to SM at 100 mcgm S/cc.; partial resistance to PAS at 100 mgm/100 cc. *Right Lower Lobe:* Sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.
A-28-51	Four cultures from 6-20-49 to 1-24-51 show partial resistance to SM at 100 mcgm S/cc. One culture on 7-25-51 shows complete resistance to SM at 100 mcgm S/cc.	*Left Lower Lobe, Right Lower Lobe, Left Lower Apex, Left Apex and Trachea:* Complete resistance to SM at 100 mcgm S/cc.; complete resistance to PAS at 25 mgm/100 cc.

RESUMEN

1) El material caseoso tuberculoso así como el fibrocaseoso puede contener bacilos tuberculosos viables en grandes números antes y después de un corto periodo del embalsamamiento. Los anatomo-patólogos, los observadores y demás del personal que maneja estos materiales deben sujetarse a las medidas de seguridad para evitar las infecciones accidentales.

2) La sensibilidad quimioterápica puede variar en el mismo individuo dependiendo del tipo de lesión y ubicación de la fuente de donde los bacilos tuberculosos se obtienen como lo demuestran nuestros datos sobre los esputos y los materiales de autopsia.

RESUME

1) La tuberculose caséeuse el fibrocaséeuse peut contenir des bacilles tuberculeux vivants en grande quantité soit avant, soit après une courte

TABLE II (Continued)

Autopsy No.	Sensitivity Results, Sputa Cultures	Sensitivity Results on Positive Autopsy Cultures
A-29-51	Fifteen cultures between 4-12-50 and 9-26-51 show partial resistance to SM at 100 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.	*Prostate and Left Upper Lobe:* Complete resistance to SM at 100 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.
A-30-51	Eight cultures between 7-13-49 and 9-6-50 show SM sensitive at 10 mcgm S/cc.; PAS sensitive at .1 mgm/100 cc.	*Right Upper Lobe:* Sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.
A-31-51	Cultures on 7-20-49 and 9-28-50 are sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc. Culture of 5-23-51 shows partial resistance to SM at 100 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.	*Right Lower Apex and Right Apex:* Sensitive to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc. *Lower Right:* Sensitive to SM at 10 mcgm S/cc.; partial resistance to PAS at .1 mgm/100 cc.
A-34-51	Thirty-three cultures between 12-16-47 and 7-11-51 show graduating partial resistance to SM; sensitive to PAS. Culture of 7-11-51 shows partial resistance to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.	*Left Lower Lobe:* Sensitive to both SM and PAS. *Emphysema* (cavity): Partial resistance to SM at 100 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc. *Seminal Vesicle:* Partial resistance to SM at 10 mcgm S/cc.; sensitive to PAS at .1 mgm/100 cc.

Note: 4+: Surface of medium entirely covered; 3+: Growth not quite confluent; 2+: Innumerable colonies; 1+: 50 to 200 colonies. Medium for sensitivity tests: Jensen-Lowenstein's modified.

Key to Table II: SM: streptomycin; PAS: para-aminosalicylic acid; mcgm S/cc: micrograms streptomycin per 1 cc. solid egg media; mgm/100 cc.: milligrams para-aminosalicylic acid per 100 cc. solid egg media; sensitive: 0 growth to 10 mcgm for streptomycin and 0 growth at .1 mgm per cent for para-aminosalicylic acid; resistant: as shown in table.

période qui suit l'embaumement. Les anatomo-pathologistes, les observateurs et autres membres du personnel utilisant ces matériaux devraient prendre des mesures de sécurité de façon à éviter les infections accidentelles.

2) La sensibilité à la chimiothérapie peut varier chez le même individu en fonction du type de la lésion et de l'origine des bacilles tuberculeux, comme nous avons pu le constater par l'examen des crachats et du matériel d'autopsie.

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Histoplasmin Sensitivity in Brazil*

JOSE SILVEIRA, M.D., F.C.C.P.
Salvador, Brazil

The high frequency of reactors to the antigen of *Histoplasma capsulatum* reported in some regions of the United States, occasioned similar researches everywhere in order to determine the distribution of this fungus.

The "Instituto Brasileiro para Investigacao da Tuberculose," trying to find the incidence of reactors to histoplasmin in the state of Bahia, Brazil, accomplished a testing program. The first antigen used was sent from Rio de Janeiro (Oliveira Lima) already diluted 1/100. Later some was obtained from the United States Public Health Service to be diluted 1/500. The final lot came from Rio de Janeiro with the recommendation that it be diluted 1/1000. The comparative results of these tests were presented and discussed in the issue of the "Arquivos do Instituto Brasileiro para Investigacao da Tuberculose," Vol. IX, fasc. II, by Artur Ventura de Matos. He came to the conclusion that the stronger the concentration, the greater the reaction. He thought that one must consider part of the reactions caused by 1/100 dilution as non-specific.

In this present work the results are limitated only to the cases tested with histoplasmin from the Public Health Service in Washington, lot H-40, sent to us by Dr. R. J. Anderson.

Together with the histoplasmin test we did the tuberculin test, with tuberculin from Rio de Janeiro (Fundacao Ataulpho de Paiva) in dilutions of 1/20,000 or 1/1,000, 1/100 and 1/10. The tests were considered positive when there was an area of induration measuring 5 mm. or more in diameter. No case of erythema was considered positive. The study included two groups: A) a group in Salvador (the capital city of the state) under the direction of Artur Ventura de Matos, composed of people who came to the Instituto Brasileiro para Investigacao da Tuberculose for examinations of the respiratory organs, young students from the university, apprentice sailors and pregnant women from the "Pro-Mater da Bahia." B) A group from the inland under the direction of Augusto Pedreira de Assis Freitas (city of Feira de Santana) composed of young school boys.

The city of Feira de Santana, is 150 km. from Salvador and has 100,000 people. It is located in the "sertao" of the State of Bahia, a dry zone with a moderate climate. Its communication with Salvador is by railway and highway. It is chiefly a cattle raising and agricultural center.

The results of histoplasmin tests made in these 895 cases are shown in Table I. The same technique was used as for the Mantoux test, in the inner part of the forearm and reading after 48 hours.

After separating the individuals by sex, color and age, a significant

*From the "Instituto Brasileiro para Investigacao da Tuberculose," Salvador, Bahia, Brazil.

TABLE I

CASES	Reactors Number	Per cent	Non Reactors Negative	Total
People in Salvador	46	13	309	355
People in the Island	106	19.6	434	540
TOTAL	152	17	743	895

majority of the males were found, as well as a frequency of little significance in negroes and mulattoes, from 15 to 30 years old.

A group from the school of apprentice sailors was tested with the same lot (H-40). They received a dilution at 1/500 and the non-reactors 48 hours later were given the dilution at 1/100. The results of this series were:

Tested at 1/500		87
Positives	19 (22 per cent)	
Negatives	68	
Tested at 1/100		65
Positives	7 (10.8 per cent)	
Negatives	58	

It is interesting to note that when two doses were used 31 per cent reacted, which is very high. Three cases were not tested, in the group of 68 negatives to the dilution at 1/500.

Editorial

THE RATIONALE OF PNEUMOPERITONEUM TREATMENT OF EMPHYSEMA

Artificial pneumoperitoneum as a useful measure in the management of hypertrophic emphysema has been gaining recognition during the past few years. In judiciously selected cases, the therapeutic results are highly satisfactory in the great majority of instances.

In the excellent paper by Kory and his associates published in this issue, a precise, objective, analytical study is presented on pulmonary function and circulatory dynamics resulting from pneumoperitoneum treatment of patients with emphysema. All interested in the clinical use of this measure should familiarize themselves with the basic, illuminating, pertinent information offered in their communication.

The intelligent application of pneumoperitoneum treatment requires a thorough understanding of the pathogenesis of this disease. Chronic hypertrophic emphysema is characterized by the following pathologic structural changes: (1) Destruction of the perialveolar and peribronchial elastic fibers. (2) Dilatation or rupture of the alveoli, with the consequent formation of large air spaces. (3) Destruction of some of the perialveolar capillaries. (4) Relative increase in the size of the lung. (5) Distention of the thoracic cage. (6) Abnormally low position of the diaphragm.

Functionally, one finds: (1) lessened negativity of the intrapleural pressure; (2) impaired, deranged diaphragmatic function; (3) decreased respiratory excursions of the ribs; (4) interference with normal blood circulation.

The development of hypertrophic emphysema is brought about by the excessive intrapulmonary pressure during severe coughing of long duration, by degenerative changes in the myoelastic elements of the lung and by partial bronchial occlusion due to bronchospasm or other pathologic changes. It is well to recall in this connection that when cough is strenuous, the intrapulmonary pressure may stand as high as from 80 to 200 mm. of mercury over and above atmospheric pressure. Chronic lung infections may lead to degenerative changes in the supportive and myoelastic elements of the lung either by direct toxic influences or by the associated perivascular fibrosis. In pulmonary infections, in allergy with the lung as the shock organ and pulmonary fibrosis of all sorts there is a tendency to reflex bronchospasm. The latter may result in a check-valve mechanism which permits the ingress of air into distal portions of the lung but prevents its egress. In this manner, the trapping of some of the air inhaled results in stretching and tearing of the alveoli. Similar check-valve effect may be caused by edema, granulation or fibrosis of the bronchial wall or by the accumulation of inflammatory exudate. The condition which develops in connection with the trapping of the air may well be designated as alveolar pneumatic hypertension.

Distention of the thorax as well as the enlargement of the lung in emphysema are brought about by the loss of elasticity of this organ. With the loss of the centripetal (hilusward) traction of the elastic elements, there is a decrease in or complete disappearance of the negativity of the intrapleural pressure. The inspiratory muscles, not being obliged to counterbalance the inward pull of the intrapleural pressure, are bound to distend the thoracic cage. The normal position of the diaphragm is the direct result of the traction force of the intrapleural negative pressure. In consequence of the disappearance of the upward-traction of the intrapleural pressure in emphysema, the diaphragm occupies a constant low (inspiratory) position. In this abnormally low position, the diaphragm is functionally handicapped or completely defunctionalized. The diaphragm is responsible for from 37 to 47 per cent of the ventilatory function of the lung. Pulmonary insufficiency resulting from derangement of diaphragmatic function is aggravated by the faulty distribution of the inhaled air. The latter is mostly drawn to the peripheral areas of the lung where large numbers of alveoli are destroyed, while the intact, centrally located alveoli receive none or only small amounts of the tidal air. Another factor which contributes to hemorespiratory insufficiency is the decrease in the return flow of venous blood from the periphery to the right auricle of the heart. Thus, smaller amounts of blood are available for oxygenation in the pulmonary capillaries. Also, diminished or absent distention of the lung on inspiration fails to dilate the pulmonary vascular bed so as to establish a gradient which normally facilitates the blood flow from the right ventricle to the lung.

Pulmonary insufficiency is corrected in emphysema by artificial pneumoperitoneum in the following manner:

1) Elevation of the diaphragm and reestablishment of approximately normal intrapleural negative pressure.

2) With more negative intrapleural pressure the size of the thoracic cage is reduced; the function of the respiratory muscles of the chest wall is enhanced.

3) More competent oxygen-carbon dioxide exchange results from the improved distribution of tidal air to anatomically and functionally intact, centrally located alveoli.

4) Blood supply to the lung through the pulmonary artery becomes more adequate.

5) Pneumoperitoneum is likely to result in reflex relaxation of spastic peribronchial smooth muscles.

6) Increased efficacy of the cough mechanism, with improved expectoration, rids the lower air passages of inflammatory exudate and insures better accessibility of the alveoli for the inspired air.

7) Maintenance of the elevated position of the diaphragm refunctionalizes this important respiratory muscle.

Artificial pneumoperitoneum has definite limitations in the treatment of hypertrophic emphysema. So as to avoid disappointment to the patient as

well as to the physician it is well to remember the following possible causes of failure with this method:

1) Anatomically and functionally irriversible, extensive loss of alveoli.
2) Widespread pulmonary fibrosis.
3) Sustained bronchospasm.
4) Diaphragmatic adhesions which prevent its elevation.
5) Atrophy of disuse of the diaphragm in long standing emphysema.
6) Heart failure which cannot be corrected.
7) Faulty technic.

In reference to technic, the importance of giving small amounts of air with each treatment cannot be overemphasized. It is mandatory to give less than 1,000 cc., preferably, from 500 to 600 cc., depending upon the size of the abdominal cavity and the depth of the position of the diaphragm. Intraperitoneal inflations which are too large are bound to immobilize the elevated diaphragm and thus defeat the purpose of treatment.

I advise my patients to wear a snuggly-fitting abdominal support. The latter reduces the size of the abdominal cavity and enhances the elevation of the diaphragm. It is worn night and day. With the use of abdominal supports lesser amounts of air are required for efficient pneumoperitoneum treatment.

Andrew L. Banyai.

College Chapter News

OKLAHOMA CHAPTER

Members of the College in the state of Oklahoma met for the first time at the Mayo Hotel, Tulsa, April 12 and organized the Oklahoma Chapter. The following were elected officers:

R. M. Shepard, Tulsa, President
Clarence E. Bates, Oklahoma City, Secretary-Treasurer.

PERUVIAN CHAPTER

Members of the Peruvian Chapter sponsored a postgraduate course in diseases of the chest in Lima, March 27-31. Physicians from Lima, the provinces, and Venezuela attended this course which was the first sponsored by the chapter.

ILLINOIS CHAPTER

The Illinois Chapter of the College, together with the Chicago Tuberculosis Society, Tuberculosis Institute of Chicago and Cook County, and the Illinois Tuberculosis Association sponsored a dinner in honor of Dr. Richard R. Trail, London, England, Medical Director of the Papworth Village Settlement and Governor of the College for Greater London, at the Drake Hotel, Chicago, May 8. Dr. William J. Bryan, President of the Illinois Chapter, presided and introduced Dr. Andrew L. Banyai, Milwaukee, Wisconsin, President of the College, and Dr. Alvis E. Greer, Houston, Texas, President-Elect. Dr. Trail spoke on "The Children of Papworth Village."

PENNSYLVANIA CHAPTER

The Pennsylvania Chapter met jointly with the Philadelphia Association of Tuberculosis Clinics at the Bellevue-Stratford Hotel, Philadelphia, May 7. Drs. Robert Charr, John S. Packard, and Thomas J. E. O'Neill participated in the program. The chapter elected the following members to office: John H. Bisbing, Reading, President; Nathan H. Heiligman, Allentown, Vice-President; John V. Foster, Harrisburg, Secretary-Treasurer.

College News Notes

Dr. Augusto Fernandez Conde, Havana, Cuba, has been elected President of the Sociedad Cubana de Tisiologia.

Dr. Joseph Sagi, Milwaukee, Wisconsin, spoke before the Milwaukee Metropolitan Section meeting, February 27, on "What ACTH and Cortisone Will Not Do in Diseases of the Chest."

Dr. Martin J. Sokoloff, Philadelphia, Pennsylvania, Chief of the Division of Tuberculosis, Philadelphia Department of Public Health, has been appointed Director of the Department of Diseases of the Chest at Jefferson Hospital, Phila.

Dr. Jean-Jacques Laurier, Montreal, Quebec, Secretary of the Quebec Chapter of the College, has been awarded the Annual Exchange Scholarship between Great Britain and Canada. Dr. Laurier will be the official delegate of the Canadian Tuberculosis Association at the Coronation of Queen Elizabeth II.

Dr. Timothy R. Murphy, Milwaukee, Wisconsin, discussed "Cardiac Catheterization in Mitral Stenosis" at the Milwaukee Metropolitan Section meeting, March 27.

The following members in Montreal, Quebec, were elected officers of La Societe de Phtisiologie de Montreal at the Hotel-Dieu, Montreal, February 20:

B. Guy Begin, President
Ruben Laurier, Vice-President
Philippe Landry, Secretary
Fernand Gregoire, Treasurer
Charles A. Messier, Assistant.

Obituary

NELSON W. STROHM

1887-1952

After a long illness, the American College of Chest Physicians lost a staunch friend and supporter in Dr. Nelson W. Strohm who passed away on October 22, 1952.

Dr. Strohm was born on December 23, 1887, near Pittsburgh, Pennsylvania. After graduation from the University of Buffalo in 1912 he soon became interested in the field of chest diseases—even before completing his internship at the Buffalo General Hospital, July, 1913. He served the Health Departments of Buffalo and Erie County in part time capacity as Examining Physician in chest diseases from 1919 to 1948 and in full time capacity as Director of Tuberculosis Control from 1948 to his death. He was Entrance Examiner for the New York State Hospital for Incipient Tuberculosis at Raybrook, New York, Consultant for the J. N. Adam Memorial Hospital at Perrysburg, New York, and a member of the Medical Staffs of the Buffalo General and the E. J. Meyer Memorial Hospitals. Early in his career he became identified with the Faculty of the Medical College of the University of Buffalo. He was an Associate in Medicine from 1927 until his death.

Dr. Strohm was a strong advocate of organized medicine as it exists today with minimal governmental interference. In 1914 he joined the Erie County Medical Society and through the years thereafter devoted much time as a committee member or chairman of many committees such as Public Health, Education, Grievance, etc., and as chairman was a member of the Comitia Minora (Executive Committee) for many years. He served as President of the Erie County Medical Society in 1941. On several occasions he had been elected delegate to the Medical Society of the State of New York, and that organization honored him with election to the post of Vice Speaker in 1949. He resigned this office in 1951 because of ill health. He was a member of the Buffalo Academy of Medicine, American Medical Association, American Public Health Association, and Trudeau Society. He was a Fellow of the American College of Physicians, and the American College of Chest Physicians.

He had a great love for and pride in the latter organization of which he was an early member. He pioneered in the formation of the second College Chapter (New York) organized in 1940, and devoted energy and means to the success of the Chapter, serving as its second president in 1941. In 1943 he was elected Regent for District No. 2 (New York) serving the College well until 1949. He loved to recall the early struggling days of the College and his old associates of that period, and in later years took great satisfaction in the growth and virility of the organization.

Dr. Strohm loved the great outdoors and as often as duties permitted he might have been found somewhere in New York, Pennsylvania or Canada with rod and reel or dog and gun. Failing health of his last few years prevented indulgence in these hobbies.

A vigorous and militant, but always fair, exponent of what he believed to be right in medical or civic organizations he will be greatly missed by a great many of the College members who worked with him and knew him intimately as well as by hosts of friends in civic, fraternal and other professional groups.

We of the College deeply mourn his passing and extend to his widow, Laura Strohm, our deepest sympathy.

Donald R. McKay, Regent.

Book Review

The Fight Against Tuberculosis. An Autobiography. By Francis Marion Pottenger. Published by Henry Schuman, Inc., New York, N. Y. 1952.

The foregoing title is that of a rather small book in which is recorded in a most fascinating manner the life story of one of America's leading physicians. It would be difficult for any medical man, after reading a few pages, to lay down the book until it was read from cover to cover. So extensive has been Dr. Potttenger's experience, and so wide his acquaintanceship with the great men of the tuberculosis movement, that the work is essentially an epitome of most of the important events from the early discoveries to the advent of antibiotics and resectional surgery. Most of these historic episodes have not only been observed by Dr. Pottenger, but many he has taken part in. His life span has covered almost all of the age of accomplishments in tuberculosis.

It would be a mistake to give the impression, however, that this is a record of a tuberculosis specialist. It is the life story of an American pioneer: of an accomplished physician, in a broad sense; of a philosopher of much merit; and of a model citizen of the free world in general and America in particular.

The early chapters are those of his ancestral origins; of his rustic heritage and early life in Ohio, involving the stern discipline of such a life. Like most of our citizens of that era there was a thrift born of necessity and a zeal to work was installed by honest, God fearing forbears. Dr. Pottenger and some of his brothers were the first to leave the soil for seven generations!

The early rustic life will no doubt bring back nostalgic feeling to those who have had similar experiences. The devout religious life, the one-room-eight-grade-school (where most everything was mentioned but the McGuffy Readers) the life on the farm; barn raisings; hog killings; the winnowing of the grain; the grinding of grist by the miller; the bartering of produce in the markets; the berry picking expeditions with the berry pies and jams; the early morning notes of the song birds, and many more events, afforded variation and interest in daily and seasonal life and gave inspiration to future achievement.

With such a beginning, Dr. Pottenger went through his childhood and adolescent years; then to Otterbein College (a United Brethren College just north of Columbus); to the Medical College of Ohio at Cincinnati where, as was the custom of the day, he studied under a preceptor and graduated in two years; to Europe for post graduate study; and on to a most interesting and useful career in medicine. By "good fortune" (Reviewer's quotes) he had weak eyes, so that he was allowed to study German and French, instead of Greek, because of the difficulty he had reading the Greek letters. This knowledge of German, in particular, gave him an entree into the inner circle of the Great Physicians of the Continent—most of whom in those days were Austrian and German. His four trips to Europe allowed him to contact nearly all the great medical teachers of the day. One who knows Dr. Pottenger can well understand his pleasant mannerism, his tactful approach (he always briefed himself on the work of the man he was about to see) and his persistence and zeal would give him audiences, apprenticeships or assistantships in most of the great clinics he chose to visit. In fact, one wonders if by

association with so many of the Gods of Medicine, he may not have imbibed some nectar himself.

Virchow, Senator, Nothnagel, Ewald, Spengler, Ghon, Gerhardt, Turban, Brauer, Von Schrotter, Henoch, Cohnheim, and most of the other great of the day were a few of his teachers. He did not meet Koch until 1908 when the latter came to the International Congress at Washington. At the earlier date Dr. Pottenger was not so much interested in tuberculosis because he was afraid of it. Even at that moment, however, his first wife, who was with him, was developing fatal tuberculosis. This sad experience gave Dr. Pottenger the "incentive" to study the disease and thus changed somewhat his medical career. It also caused him to move to California, on the advice of his family physician in Cincinnati. His presence in California created a great impetus to anti-tuberculosis work in the State, and his sanitorium became known throughout the world.

On several trips to Europe, Dr. Pottenger visited most of the big clinics of Austria, Germany, England, France and Italy. In England he met Bulloch, Evans, Sir James MacKenzie and others; Sir Robert Phillip he met in Scotland; Marigliano in Italy and visited Calmettes Laboratory in Paris. He observed the "rest and exercise" of Brehmer, and the "rest without exercise" of Dettweiler. He attended the various International Congresses and was present when Von Behring challenged Koch's theory of the difference between the Human and Bovine type of tubercle bacillus. He was in the midst of Ghon's and Pirquet's great studies which verified the earlier "laws" of Parrot. In 1908 the subject of bovine and human tubercle bacillus was renewed at the Eighth Congress in Washington and largely clarified. A long roster of notables entered into the discussion including Landousy, Arloing, Theobald Smith, Ravenal, Bang, Calmette, Tendeloo, Biggs and others. Theobald Smith's epochal work had thrown the balance in favor of Koch's theory—in fact clinched the argument.

As to Dr. Pottenger's own publications, consisting of eight books and over 200 papers, spread over a period of more than 50 years, his outstanding original contributions have been on physical diagnosis. His superb training by Senator, Ortner, Chvostek and other great clinicians had prepared him for a development of a most refined technic in inspection and palpation. By light touch he was able to outline densities within the chest and by observation and light touch he could detect underlying acute and chronic disease—in acute disease, by reflex muscle spasm and in chronic disease by atrophy of the overlying muscles.

The medical profession has not been too ready to recognize these achievements and some ungenerous comments might suggest that his "free imagination" of boyhood had not been curbed after all. The best reply to such criticism is that Semmelweiss' discovery was never recognized while he lived; that Forlinini only received recognition in the nick of time before his death, and that the "Great" Virchow never accorded Koch and Pasteur any recognition at any time. Critics of Pottenger's work by average physical diagnosticians might be compared to an "artist" of tin-pan-alley criticizing a virtuoso. The only bad feature is that, unlike Koch's discovery, the "machine age" of medicine has gradually pushed the method into obsolescense, along with the differentiation of liver disease by the tint of the jaundice and the diagnosis of so many diseases by odor alone. Like "Alt Wien," the age of the great "physicial diagnosticians" is gone forever, with only a few exponents left.

Another type of clinician has arisen who combines hurried observations, palpations and percussion with the information of the "mechanical brains" and arrives at the diagnosis by induction, rather than relying so much on the training of special senses. Also, like "Alt Wien," there is much regret at the passing of such a noble art and it is to be hoped, yes, it is imperative, that in the new art of "machine diagnosis," the human being with his appearance and "feel" must not be disregarded.

Dr. Pottenger's theories of the cause of the respiratory murmur is not on such

solid ground as his other work, but still is from the mature thinking of a master diagnostician.

As an organizer and promoter of Medical Activities and especially as a teacher he has few equals. He was a moving force in the organization of the American College of Physicians; various Endocrine Societies, and many more, related to climate, tuberculosis, etc.

As a teacher he correctly considers tuberculosis an "expanding" subject, a part of all medicine, rather than an individual specialty. The treatment of the disease tuberculosis has become active and not the passive method of former years. It involves physiology, chemistry, psychosomatic and other scientific means, not the morbid anatomy approach of the last century.

Dr. Pottenger has lived a rich and full life. He has met "triumph and disaster" and has always kept his poise and youthful attitude. He has appreciation of the finer attributes of life revealed in great art, literature, music, drama and philosophy. He is the patron of them all.

He has gained a philosophy that is well summed up in his last chapter "My Eighty Years," which is worthy of the best philosophy of the ages. His antidote for old age is keeping an open mind and living in the present and future not in the past. And finally he says: "I have no fear of death. It is often ruthless. Again it is a great blessing. I have had a full life. If I knew this was my last year or month or day of life, I would be sorry only because it would take me from my family and friends and terminate the possibility of completing many unfinished tasks."

The publisher, Henry Schuman, Inc., has performed a creditable task for such a book. An index of names would have made it more useful for reference work, although it is adequate for pleasurable reading for which it was intended.

Henry C. Sweany.

ANNOUNCEMENTS

The Laennec Society of Philadelphia awards an annual prize of $200 for the best paper submitted in any field related to diseases of the chest. This prize is open to undergraduates, interns, residents, or Fellows throughout the United States. The work should be original and not a review of literature or of previous contributions. The Society does not reserve the right of publication but requests that the prize-winning paper be presented at one of its regular scientific meetings.

Five copies of the manuscript should be submitted in the customary form for publication, i.e. double-spaced and with wide margins. They should be in the hands of the Secretary of the Society, Dr. Charles M. Morris, 3401 North Broad Street, Philadelphia 40, Pennsylvania, by October 1, 1953.

The Department of Otolaryngology, University of Illinois College of Medicine, announces its Annual Assembly in Otolaryngology, divided into two sections:

A. Basic Section, September 21 through 26, 1953, devoted to surgical anatomy and cadaver dissection of the head and neck, and histopathology of the ear, nose, and throat, under the direction of Dr. M. F. Snitman.

B. Clinical Section, September 28 through October 3, 1953, consisting of lectures and panel discussions, with group participation of otolaryngological problems and current trends in medical and surgical management.

Registration will be limited. Applications for attendance at one or both sections will be optional. For information write to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

DISEASES OF THE CHEST

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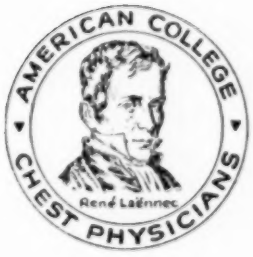

VOLUME XXIII

JANUARY - JUNE, 1953

DISEASES *of the* CHEST

OFFICIAL PUBLICATION
OF THE
AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
112 East Chestnut Street, Chicago 11, Illinois
MURRAY KORNFELD, *Managing Editor*

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COLLEGE EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

Interim Session, Semi-Annual Meeting, Board of Regents, St. Louis, Missouri, November 29-30, 1953.

20th Annual Meeting, American College of Chest Physicians, San Francisco, California, June 17-20, 1954.

3rd International Congress on Diseases of the Chest, Barcelona, Spain, Fall of 1954.

POSTGRADUATE COURSES

8th Annual Postgraduate Course on Diseases of the Chest, Knickerbocker Hotel, Chicago, Illinois, September 28 - October 2, 1953.

6th Annual Postgraduate Course on Diseases of the Chest, Hotel New Yorker, New York City, November 2-6, 1953.

MEDICAL SERVICE BUREAU

POSITION WANTED

Physician, age 44, F.C.C.P., experienced in chest diseases and modern treatment of tuberculosis, with extensive background in surgery and general medicine; able and experienced bronchoscopist—desires association with group or with individuals in southwest, preferably Texas or Arizona. Available now. Please address all inquiries to Box 277B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Staff physician wanted, 180 bed tuberculosis hospital. American graduate only, eligible for Michigan license. Salary $7,500 to $10,000, depending on qualifications and experience. Address Box 263A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Staff positions: open at state tuberculosis sanatorium in Pacific Northwest for general or special physicians. Give full qualifications, training, etc. Address Box 265A, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Ill.

Wanted—Staff Physician for approved County Tuberculosis Hospital, American citizenship and Ohio License necessary. Attractive salary. Please address all inquiries to Box 266A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Medical director wanter for 100-bed unusually active tuberculosis hospital in southern Illinois. Sanitarium presently staffed by surgeon but has a vacancy for a medical director and a resident. Institution two years old and extremely well-equipped. Please address all inquiries to Box 267A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Assistant Medical Director wanted for 225 bed sanatorium in Birmingham, Alabama. For details write Arthur J. Viehman, M.D., Superintendent, Jefferson Tuberculosis Sanatorium, Birmingham 9, Alabama.

Medical Director wanted. Tuberculosis experience essential. Attractive salary, modern home, hospital approved by American College of Surgeons. The hospital is Kalamazoo County owned and has 50 beds for tuberculosis, 12 beds for county convalescent cases (female only), and 19 beds for contagious cases. Make application read, Attention: Chairman, Board of Trustees, Fairmount Hospital, Kalamazoo, Michigan.

Always ready to abort the Bronchospasm

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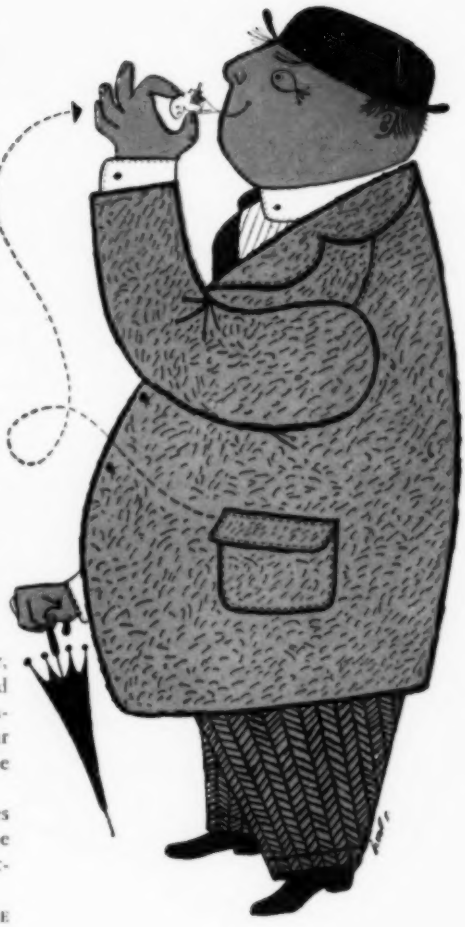
in pocket or purse



With this quick-acting bronchodilating powder, it is now possible for many chronic asthmatics to lead useful, happy lives. When the asthmatic feels a bronchospasm impending he can merely take three or four inhalations of Norisodrine Sulfate Powder and the attack usually subsides at once.

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ABBOTT'S POWDER INHALER

1. Kaufman, R., and Farmer, L. (1951), Norisodrine by Aerohalor in Asthma, Ann. Allergy, 9:89, January-February.
2. Swartz, H. (1950), Norisodrine Sulphate (25 Per Cent) Dust Inhalation in Severe Asthma, Ann. Allergy, 8:488, July-August.
3. Krasno, L., Grossman, M., and Ivy, A. (1949), The Inhalation of 1-(3',4'-Dihydroxyphenyl)-2-Isopropylaminoethanol (Norisodrine Sulfate Dust), J. Allergy, 20:111, March.

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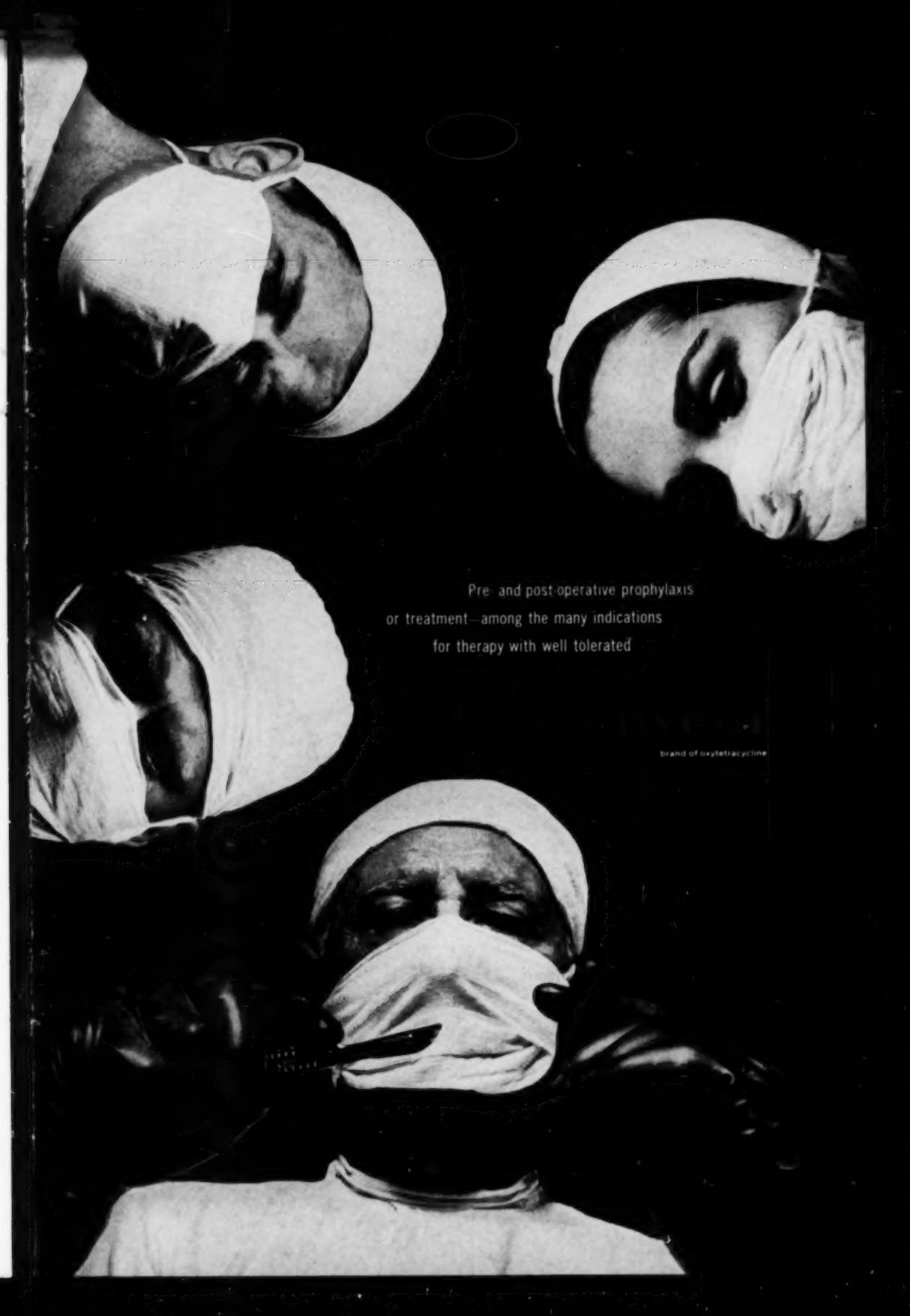
Pre- and post-operative prophylaxis
or treatment—among the many indications
for therapy with well tolerated
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THE Panray CORP

Notes on TUBERCULOSIS CHEMOTHERAPY

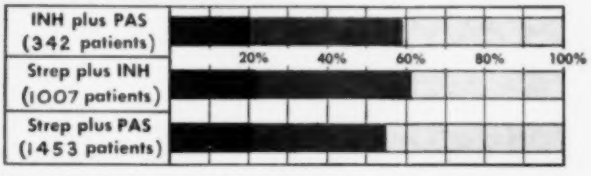
June, 1953

Further Notes on 12th TB Conference

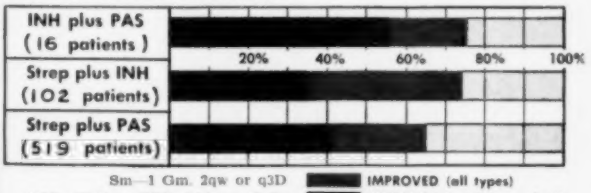
The following graphs were derived from tables prepared by the government and distributed at the 12th VA-Army-Navy Conference last February. In all, 2175 patients were treated—with isoniazid alone, INH and streptomycin, INH and PAS, and strep and PAS. Here are some interesting results:

X-Ray Results; Sm-sensitive cases

I. 2-5 MONTHS TREATMENT



II. 5-10 MONTHS TREATMENT



Sm—1 Gm. 2qw or q3D
PAS—12 Gm.; INH—300 mg. daily
IMPROVED (all types)
IMPROVED (mod. to marked)

Obviously, one cannot draw rigorous conclusions from 16 cases, but the results certainly indicate further study. In fact, "triple-threat" therapy (strep+PAS+INH) is now being studied in many institutions, and appears to give the most rapid improvement (X-ray and sputum) of all.

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10 Gm.	250 mg.	20	28	5
8½Gm.	**212½mg.**	**17**	**24**	**4¼**
8 Gm.	200 mg.	16	22	4

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